Allergy and Sleep

Basic Principles and Clinical Practice

Anna Fishbein
Stephen H. Sheldon
Editors

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Editors
Anna Fishbein
Northwestern University
Feinberg School of Medicine
Ann & Robert H. Lurie Children's
Hospital of Chicago
Chicago, IL
USA

Stephen H. Sheldon
Northwestern University
Feinberg School of Medicine
Ann & Robert H. Lurie Children's
Hospital of Chicago
Chicago, IL
USA

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Preface

The idea for this textbook arose during the implementation of our interdisciplinary allergy/sleep disorders clinic at the Ann & Robert H. Lurie Children's Hospital of Chicago. In this clinic, we identify many children with allergic diseases, such as allergic rhinitis, asthma, atopic dermatitis, and other immunologically related problems that also have principal sleep-related complaints. In managing both allergic and sleep disorders, we gained insight into the impact these disciplines have upon each other. Comprehensive management requires attention to the underlying allergic disorder as well as identification and management of sleep-related problems. On the other hand, many children presenting to the Pediatric Sleep Medicine Center at Lurie Children's Hospital have comorbid allergic symptomatology. Treatment only of the sleep-related difficulties does not result in optimal control of symptoms. Only after treatment of both the sleep-related difficulties and allergic pathology can treatment be personalized and optimized. This does not imply broad allergy testing in sleep patients but rather a symptom-directed approach.

In diagnosing and managing both sleep and allergic disorders, the practitioner must recognize important relationships. First, primary sleep-related abnormalities may affect daytime functioning caused by pathologic processes during sleep or may exacerbate existing primary medical disorders. Through diagnosis and treatment of sleep-related abnormalities, adverse health outcomes might be avoided or treatment of the primary medical problem more effective. Second, sleep-related pathology can exist concomitantly with an allergic disorder. This requires therapeutic approaches to comorbid conditions in order to obtain an optimal outcome. Finally, the presence of sleep-related abnormalities occurring as a result of allergic disorders not only impacts the health and well-being of the affected individual but can have more widespread effects on the entire family, particularly in pediatrics. A child's nocturnal sleep disruption can cause sleeplessness, daytime fatigue, and significant diurnal performance difficulties.

Although our training is in pediatrics, authors of this book are experts in pediatric and adult disease and provide an overview of disease assessment and treatment approaches throughout the life-span. Chapter authors reflect the multidisciplinary practitioners required to assess and treat allergy and sleep disorders – allergists, sleep medicine physicians, otolaryngologists, dermatologists, primary care physicians, pharmacists, psychologists, dentists, and other researchers.

The book structure reflects our overall approach to comprehensive allergy and sleep care. First, in Part I, we provide a primer on the science of sleep, allergy, immunology, circadian rhythms, and circadian immunology. In Part II, the clinical science is addressed first by presenting symptoms in a case-based approach. Next, we address assessment and treatment by specific, common allergic diseases. Finally, disease, sleep, and circadian specific therapeutics are reviewed.

Researching the association of allergy and sleep-related disorders led us to a paucity of literature. It is clear from clinical practice that children and adults with allergic disorders sleep poorly. In our sleep medicine center, it is common to see children with sleep disorders also suffer from allergy. When choosing topics for chapters to include in this text, there were many with abundant literature from which to draw. Still other topics revealed minimal evidence. It was decided to still include these chapters to begin discussion of the topic and overlap. It was not to provide answers but to stimulate questions for discussion and future research.

It is hoped this textbook will provide insight into cause and effect as well as an understanding of the complex interactions healthcare practitioners face in order to provide optimal care to their patients and families.

Chicago, IL, USA Anna Fishbein
Chicago, IL, USA Stephen H. Sheldon

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Contributors

Sabra M. Abbott, MD, PhD Department of Neurology, Northwestern University, Chicago, IL, USA

Andrew M. Abreo, MD Division of Allergy, Pulmonary, and Critical Care, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

Hrayr Attarian, MD Department of Neurology, Sleep Medicine, Northwestern Medicine, Feinberg School of Medicine, Chicago, IL, USA

Fuad M. Baroody, MD, FACS Department of Surgery, Section of Otolaryngology-Head and Neck Surgery and Department of Pediatrics, The University of Chicago Medicine and The Comer Children's Hospital, Chicago, IL, USA

Katalina Bertran, MD Department of Pediatric Cardiology and Pulmonology, Division of Pediatrics and Sleep Medicine Center, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile

Kevin L. Boyd, DDS, MSc Dentistry for Children and Families, Chicago, IL, USA
Ann & Robert H. Lurie, Children's Hospital of Chicago, Chicago, IL, USA

Pablo E. Brockmann, MD, PhD Department of Pediatric Cardiology and Pulmonology, Division of Pediatrics and Sleep Medicine Center, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile

Daniel Cerrone, MD Division of Pulmonology and Sleep Medicine, Children's Hospital Los Angeles, Los Angeles, CA, USA

Danna Chung, MD Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Christopher Cielo, DO, MS Sleep Center, Department of Pulmonary Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA

Camil Correia, MD Department of Surgery, Section of Otolaryngology-Head and Neck Surgery, The University of Chicago, Chicago, IL, USA

Maria Teresa Coutinho, PhD Child and Family Psychiatry & Pediatrics, Brown Medical School, Bradley/Hasbro Children's Research Center, Providence, RI, USA

Linda Cox, MD Department of Medicine, University of Miami at Holy Cross Hospital, Fort Lauderdale, FL, USA

Innessa Donskoy, MD, FAAP Department of Pediatric Sleep Medicine, Advocate Children's Hospital, Park Ridge, IL, USA

Henry Ehrlich, BA Pediatric Allergy and Immunology, Jaffe Food Allergy Institute, Center for Integrative Medicine for Immunology and Wellness, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Paul Ehrlich, MD Department of Pediatrics, New York University Langone Medical Center, New York, NY, USA

Anna Fishbein, MD, MSci Division of Allergy & Immunology, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Kourtney G. Gardner, MD Division of Allergy, Pulmonary, and Critical Care, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

Emily Gillett, MD, PhD Division of Pulmonology and Sleep Medicine, Children's Hospital Los Angeles, Los Angeles, CA, USA

Chris Gouveia, MD Department of Otolaryngology, Head & Neck Surgery, Northwestern Memorial Hospital, Chicago, IL, USA

David Gozal, MD, MBA Department of Child Health, University of Missouri School of Medicine, Columbia, MO, USA

Rui Guan, MD Institute of Neurological Sciences, Prince of Wales Hospital, University of New South Wales, Sydney, NSW, Australia

Jonathan A. Hemler, MD Division of Allergy, Immunology, and Pulmonary Medicine, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN, USA

Namita Jain, MD, MPH Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Natalia M. Jasiak-Panek, PharmD, BCPS Department of Pharmacy, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Anjeni Keswani, MD, MSCI Division of Allergy/Immunology, Department of Medicine, GW School of Medicine and Health Sciences, Washington, DC, USA

Fatima S. Khan, MD Department of Allergy and Immunology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Leila Kheirandish-Gozal, MD, MSc Department of Child Health Research Institute, University of Missouri School of Medicine, Columbia, MO, USA

Sofia Konstantinopoulou, MD Division of Pulmonary Medicine, Department of Pediatrics, Sheikh Khalyfa Medical City, Tibbiyya, Abu Dhabi, United Arab Emirates

Sanjeev V. Kothare, MD Pediatric Sleep Program, Department of Neurology, NYU Langone Medical Center, New York, NY, USA

Lacey L. Kruse, MD Departments of Pediatrics and Dermatology, Northwestern University Feinberg School of Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Kevin T. Le, PharmD, BCPS Department of Pharmacy, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Xiu-Min Li, MD Department of Pediatrics, Pediatric Allergy and Immunology, Jaffe Food Allergy Institute, Center for Integrative Medicine for Immunology and Wellness, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Mahboobeh Mahdavinia, MD, PhD Allergy and Immunology Division, Department of Internal Medicine, Rush University Medical Center, Chicago, IL, USA

Anne Maitland, MD Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Roneil G. Malkani, MD, MSCI Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Laurie A. Manka, MD Division of Pulmonary, Critical Care, and Sleep Medicine, National Jewish Health, Denver, CO, USA

Richard J. Martin, MD Department of Medicine, National Jewish Health, Denver, CO, USA

Daphne Koinis Mitchell, PhD Child and Family Psychiatry & Pediatrics, Brown Medical School, Bradley/Hasbro Children's Research Center, Warren Alpert Medical School of Brown University, Providence, RI, USA

Thomas Moran, PharmD, BCPS Department of Pharmacy, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Anne Marie Morse, DO Department of Child Neurology, Sleep Medicine, Geisinger Medical Center, Janet Weis Children's Hospital, Danville, PA, USA

Sukhraj Mudahar, PharmD, BCPS Department of Pharmacy, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Tanvi H. Mukundan, MD Department of Sleep Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Luis E. Ortiz, MD Sleep Center, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Nurcicek Padem, MD Division of Allergy & Immunology, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University, Chicago, IL, USA

Rafael Pelayo, MD Department of Psychiatry and Behavioral Sciences, Stanford Center for Sleep Sciences and Medicine, Stanford Sleep Medicine Center, Redwood City, CA, USA

Barry J. Pelz, MD Division of Asthma, Allergy, and Clinical Immunology, Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI, USA

Matthew Purkey, MD Department of Otolaryngology, Head & Neck Surgery, Northwestern Memorial Hospital, Chicago, IL, USA

Oriana Sanchez, MD Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Trinidad Sánchez, MD Department of Pediatric Cardiology and Pulmonology, Division of Pediatrics and Sleep Medicine Center, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile

James W. Schroeder Jr., MD Department of Surgery, Division of Otorhinolaryngology, Head and Neck Surgery, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Department of Otorhinolaryngology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Sophie Shay, MD Division of Otolaryngology-Head and Neck Surgery, Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern McGaw Medical Center, Chicago, IL, USA

Stephen H. Sheldon, DO, FAAP Departments of Pediatrics & Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Sleep Medicine Center, Division of Pulmonary and Sleep Medicine, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Vinaya Soundararajan, MD Department of Dermatology, Northwestern University, Chicago, IL, USA

Bruce Tan, MD Department of Otolaryngology, Head & Neck Surgery, Northwestern Memorial Hospital, Chicago, IL, USA

Hui-Leng Tan, MBBChir, MD Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, London, UK

Ignacio E. Tapia, MD, MS Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Sleep Center, Division of Pulmonary Medicine, The Children's Hospital of Philadelphia, Philadelphia, PA, USA

Erin Thanik, MD, MPH Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Irina Trosman, MD Sleep Medicine Center, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Samuel J. Trosman, MD Department of Otolaryngology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Charlie Tyack, DClinPsy Sleep Medicine Department, Evelina London Children's Hospital, Guy's & St Thomas' NHS Foundation Trust, London, UK

Sally Ward, MD Division of Pulmonology and Sleep Medicine, Children's Hospital Los Angeles, Los Angeles, CA, USA

Joshua B. Wechsler, MD Division of Gastroenterology, Hepatology & Nutrition, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Julia A. Wisniewski, MD Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Manisha Witmans, MD, FRCPC, FAASM Division of Pediatric Pulmonology, Department of Pediatrics, The Stollery Children's Hospital & University of Alberta Hospitals, Edmonton, AB, Canada

Duri Yun, MD, MPH Departments of Pediatrics and Dermatology, Northwestern University Feinberg School of Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Phyllis C. Zee, MD, PhD Department of Neurology, Northwestern Medicine Feinberg School of Medicine, Chicago, IL, USA

Part I

Science of Sleep

Sleep, Sleep Disorders, and Immune Function

1

Hui-Leng Tan, Leila Kheirandish-Gozal, and David Gozal

In this introductory chapter, our aim is not to provide comprehensive coverage of the topic, but rather highlight tantalizing snippets of interesting information regarding the paradigm of the busy cross talk between sleep, sleep disorders, and immune function, in the hope that it will pique the interest of the reader and stimulate further reading.

Sleep and Immune Function

Immunological processes are regulated by sleep and circadian rhythms [1]. During sleep, downregulation of the hypothalamus–pituitary-adrenal (HPA) axis and reduced activity of the sympathetic nervous system (SNS) occur. Levels of cortisol, epinephrine, and norepinephrine decrease, whereas levels of growth hormone (GH), leptin, and prolactin increase. All of these hormones and many others support immune cell activation, proliferation, and differentiation and the production of pro-inflammatory cytokines such as IL-1, IL-12, TNF-α, and IFN-γ. Immune rhythms are also regulated by intrinsic cellular clocks which arise from conserved transcription-translation feedback oscillator loops driven by a set of dedicated clock proteins. These circadian clocks regulate the rhythms of inflammatory processes by

H.-L. Tan
Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, London, UK
e-mail: H.Tan@rbht.nhs.uk

L. Kheirandish-Gozal (✉)
Department of Child Health Research Institute, University of Missouri School of Medicine, Columbia, MO, USA

D. Gozal
Department of Child Health, University of Missouri School of Medicine, Columbia, MO, USA

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selectively intruding into immune pathways and orchestrate the phenotype and specific activity of multiple cells including macrophages, lymphocytes, and natural killer cells.

In accordance with such circadian-immune interactions, differentiated immune cells such as cytotoxic NK cells and terminally differentiated cytotoxic T lymphocytes increase their presence and activity during the day with increased prolonged wake periods. Since their activation can occur as a rapid response pattern and very quickly, this unique setup allows for the efficient and speedy combat of intruding antigens and organisms that are more likely to occur during the active waking phase. In contrast, undifferentiated or less differentiated immune cells, such as naïve and central memory T cells, peak during the night, when the more slowly evolving adaptive immune responses are initiated and propagated. Sleep, particularly slow-wave sleep, i.e., the predominant stage of sleep during the first half of the night, promotes the release of GH and prolactin, while cortisol and catecholamines are at trough levels. These conditions support not only the shift of the Th1/Th2 cytokine balance toward that of Th1 but also enable the enhanced production of IL-12 by antigen-presenting cells, a process that is essential for the activation of T helper cells and an increase in T helper cell proliferation. Herein lies an important facet of the role of sleep in the formation and maintenance of immunological memory [2]. By the time one reaches the end of a night's sleep in the early hours of the morning, Th2 activity predominates [3]. From such observations, it follows that perturbation to sleep integrity, cycling, or duration is likely to alter this finely regulated and coordinated set of immune interactions, leading to disruption of the immune homeostatic processes.

Interestingly, the relationship between the immune system and sleep is bidirectional, such that the immune response can reciprocally impact on sleep. For example, many infectious processes, particularly during the acute phase of the immune response, result in an increase in the duration of NREM sleep and concomitant decrease in REM sleep and wakefulness [4]. Cytokines such as IL-1β and TNF-α are produced as part of the acute phase immune response and can induce symptoms of fatigue and sleepiness and also promote non-rapid eye movement sleep [5]. This is postulated to be a mechanism by which organisms divert energy resources toward mounting a robust response against the infective challenge, and as such increased sleep activity is likely to improve the specific antimicrobial immune function response.

Sleep Deprivation and Its Impact on Immune Function

A substantial portion of our understanding on the relationship between sleep and the immune system has been derived from experiments which curtail the duration of sleep in experimental subjects. The impact of acute sleep deprivation differs from that of chronic sleep restriction or deprivation. Prolonged sleep curtailment invokes the non-specific persistent production of pro-inflammatory cytokines, resulting in a

state of chronic low-grade systemic inflammation, while concomitantly impairing host defense mechanisms, both of which have significant detrimental effects on health. Low-grade systemic inflammation is one of the common themes that will be pervasively invoked throughout this chapter and is a risk factor for cognitive, cardiovascular, and metabolic morbidity, especially when present in conjunction with obesity, another common condition in which low-grade systemic inflammation is frequently detected.

It is a commonly held lay view that inadequate sleep makes one more prone to catching colds. This supposedly "old wives' tale" is actually supported by experimental models. Prather et al. recruited 164 healthy adult volunteers, objectively assessed their sleep duration for a week, then quarantined them, and administered nasal drops containing rhinovirus [6]. Participants who had shorter sleep duration (<6 h) prior to inoculation had an increased likelihood of developing clinical cold symptoms. This work supported similar findings from a prior study by Cohen and collaborators, based on self-reported sleep duration [7]. Consistent with these experimental findings, analysis of data from National Health and Nutrition Examination Surveys (NHANES) in US adults revealed that self-reported short sleep duration, a physician's diagnosis of a sleep disorder, or reported trouble with sleeping were all associated with a greater likelihood of a common cold, infection, or both in the 30 days prior to the survey [8].

To return to the previously alluded topic of immunological memory, sleep has been shown to have an impact on vaccine responses. Restricting sleep for a week prior to administration of the influenza vaccine significantly reduced the effectiveness of the vaccine response and the generation of neutralizing antibodies to the antigen epitopes of the vaccine [9]. Similarly, subjects who had regular sleep after hepatitis A vaccination (HAV) displayed a nearly twofold higher HAV antibody titer after 4 weeks when compared to subjects who were kept awake on the night prior to the administration of the vaccine [10]. Under real-life conditions, shorter sleep duration predicted a decreased likelihood of being clinically protected from hepatitis B at the conclusion of the three doses of hepatitis B vaccination series [11].

Shift Work and the Immune System

A growing number of epidemiological studies have linked night shift work to increased risk of cancer, presumably secondary to circadian disruption. Night shift work has been shown to be associated with epigenetic modifications of key circadian genes, some of which can act as transcriptional regulators, altering the expression of cancer-related susceptibility genes and gene networks regulating cell division and DNA repair [12]. It has also been postulated that the suppression of melatonin from nighttime light exposure further contributes to the environmental milieu favoring tumorigenesis, as melatonin can be oncostatic. Indeed, as far back as 2007, the WHO recognized this epidemiologic evidence and classified night shift work as a probable carcinogen.

Poor Sleep Quality and Telomeres

Prather et al. hypothesized that accelerated cellular aging, as indicated by telomere attrition in immune cells, may explain the association between poor sleep quality with increased incidence and progression of a number of chronic health conditions, particularly in obese individuals [13]. They showed that in obese adults, poorer global sleep quality, measured by the Pittsburgh Sleep Quality Index (PSQI), was associated with shorter telomere length in T lymphocytes.

Obstructive Sleep Apnea

Here we will take advantage of a rather extensive body of work in a highly prevalent sleep disorder, namely, obstructive sleep apnea (OSA), to illustrate some of the concepts briefly discussed above and to further explore a few of the themes in greater detail. OSA is now recognized as one of the most common sleep disorders in childhood as well in adulthood. Estimates of prevalence in pediatric populations vary depending on the country or ethnic groups evaluated as well as on the stringency of the diagnostic criteria used but typically range between 1% and 5% and can be appreciably higher in certain high-risk groups. It is defined as partial or complete obstruction of the upper airway during sleep, potentially resulting in oxygen desaturations and hypercapnia, increased respiratory effort with intrathoracic pressure swings and sleep fragmentation. The various relationships between pediatric OSA and immune function are closely entwined (for more details see chapter on Sleep-Related Breathing Disorders and Inflammation).

Firstly, immune cells play an important role in the etiology of pediatric OSA. OSA etiology is typically multifactorial, and pathophysiological factors are often empirically divided into anatomical factors that effectively reduce airway caliber and factors which increase upper airway collapsibility. Immune cells potentially contribute to both. One of the commonest etiological factors in pediatric OSA is adenotonsillar hypertrophy. The exact mechanisms underlying follicular lymphoid proliferation and hyperplasia of the tonsils and adenoids remain poorly understood. However, when tonsillar tissues from children with OSA are cultured in vitro, the proliferative rates of the associated cluster of differentiation (CD)3, CD4, and CD8 cells were higher compared with tonsillar tissues from children with recurrent tonsillitis. Pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1α were also more highly expressed in the OSA-derived tonsils. It has been postulated that respiratory viruses and possibly recurrent vibration of the upper airway wall from snoring may promote localized inflammation and perpetuate specific immune memory mechanisms that are more likely to be activated in the context of recurring viral stimuli prompting the accelerated proliferation and enlargement of the adenoids and tonsils and thereby facilitating upper airway obstructions during sleep. Inflammatory conditions affecting the upper airways, such as allergic rhinitis and asthma, can also contribute to increased upper airway collapsibility.

Medical therapy for OSA, particularly when mild, is therefore centered around immune modulators, namely, leukotriene-receptor antagonists (such as montelukast) and intranasal corticosteroids. There is increased expression of cysteinyl leukotriene receptors in tonsils from children with OSA compared with children with recurrent tonsillitis [14]. These leukotriene receptors have been shown to be expressed by tonsillar T cell lymphocytes [15]. Application of leukotriene antagonist to an in vitro tonsillar cell culture system (obtained from children with OSA) elicited dose-dependent reductions in cell proliferation and reductions in the secretion of the cytokines TNF-α, IL-6, and IL-12 [16]. These results suggest that leukotriene pathways mediate intrinsic proliferative and inflammatory signaling pathways in adenotonsillar tissues from children with OSA, and targeted pharmacologic disruption of these pathways serves as a viable treatment option. Indeed, studies where children with mild OSA received a treatment course of montelukast have resulted in significant reductions in adenoidal size and improvement of their OSA severity [17, 18].

Similarly, the addition of corticosteroids in vitro to the tonsillar cell culture system resulted in decreased proliferative rates and increased apoptosis and reduction in the secretion of the pro-inflammatory cytokines IL-6, IL-8, and TNF-α [19]. A randomized crossover trial of 6-week treatment with intranasal budesonide for mild OSA showed reductions in the severity of OSA as well as in the size of adenoidal tissues. Importantly, discontinuation of therapy for 8 weeks did not result in the occurrence of rebound symptoms [20].

Obstructive Sleep Apnea and Inflammation

OSA can promote the activation and propagation of systemic inflammatory responses [21]. Microarray analyses of mRNA from peripheral leukocytes isolated from children with OSA has revealed the coordinated recruitment of gene clusters involved in the regulation and propagation of inflammatory pathways [22]. Studies have demonstrated the elevation of plasma levels of pro-inflammatory cytokines such as IL-6, IFN-γ, and TNF-α in children with OSA, while levels of the anti-inflammatory cytokine IL-10 are reduced, thereby shifting the balance even further toward a pro-inflammatory state [23–26]. One potential mechanism of such findings may reside in the occurrence of epigenetic modifications within regulatory T lymphocyte (Tregs) subsets. The promoter region of the *FOXP3* gene, which controls the transcriptional fate and differentiation of lymphocytes into Tregs, exhibits OSA severity-dependent increases in methylation in affected children [27]. Such epigenetic alterations have subsequently been linked to the presence of reduced Treg counts in the peripheral blood of children with OSA [28]. Considering the significant role Tregs play in the suppression of inflammation, it is postulated that differentially orchestrated responses of various tissues to OSA-induced perturbations may interact with environmental and intrinsic genetic factors to elicit a spectrum of inflammatory phenotypes linked to end-organ morbidities [29].

OSA and Asthma

The prevalence of children snoring and scoring positive for sleep-disordered breathing in the pediatric sleep questionnaire is higher in asthmatic children than in non-asthmatic children and increased with increasing asthma severity [30]. Kheirandish-Gozal et al. demonstrated that prevalence of polysomnographically proven OSA is indeed higher in children with poorly controlled asthma. Furthermore, asthma control was improved following effective treatment of OSA [31]. Bhattacharjee et al. took this a step further and studied asthma control of 13,506 asthmatic children in the USA who underwent adenotonsillectomy via electronic database analysis, comparing their asthma control the year prior to surgery with the year following the surgical procedure [32]. The authors found a 30% reduction in asthma exacerbations, a 25% decrease in the number of asthma-related emergency room visits, and a 36% reduction in asthma-related hospital admissions after adenotonsillectomy. In contrast, there was just a 2% reduction in asthma exacerbations seen in the 27,012 age-, sex-, and geography-matched control children with asthma who did not undergo adenotonsillectomy. A systematic review of the literature also found clinically significant reductions in markers of asthma severity after adenotonsillectomy, i.e., when the two conditions coexist, treatment of the OSA can be associated with improved asthma control [33]. When adult patients with asthma who had moderate/severe OSA were treated with CPAP, their asthma control, quality of life, and lung function were markedly improved [34]. These findings have prompted many respiratory centers to start screening for OSA in their difficult asthma programs. Of note, asthma has also been identified as one of the risk factors for residual OSA post adenotonsillectomy [35].

It is worth highlighting that there was a high proportion of obese children in the abovementioned study cohorts. Obesity is an important risk factor for OSA, and both are conditions where there is low-grade systemic inflammation [36]. When OSA was successfully treated in obese children with OSA, IL-6, IL-18, PAI-1, MCP-1, MMP-9, adropin, and leptin plasma levels decreased, whereas adiponectin levels increased [37]. These improvements were not seen in the 30 children in whom there was residual OSA. This study would suggest that in obese children, not only does OSA amplify the underlying systemic inflammatory pathways that have been a priori been activated by obesity, but more importantly, effective treatment of the OSA results in improvement in the overall inflammatory status. An epidemiological link has also been described between obesity and asthma, thereby suggesting an interplay between the three conditions [38].

The mechanisms underlying the link between OSA and asthma are still poorly understood. The united airway hypothesis [39] postulates that inflammation of the upper airway from OSA may exacerbate inflammation in the lower airways, with resultant deterioration in asthma control. Conversely, exhaled breath condensate containing inflammatory cytokines originating from the lower airways in poorly controlled asthmatics may initiate or contribute to the proliferation of upper airway lymphoid tissues and also promote upper airway collapsibility, and thus OSA.

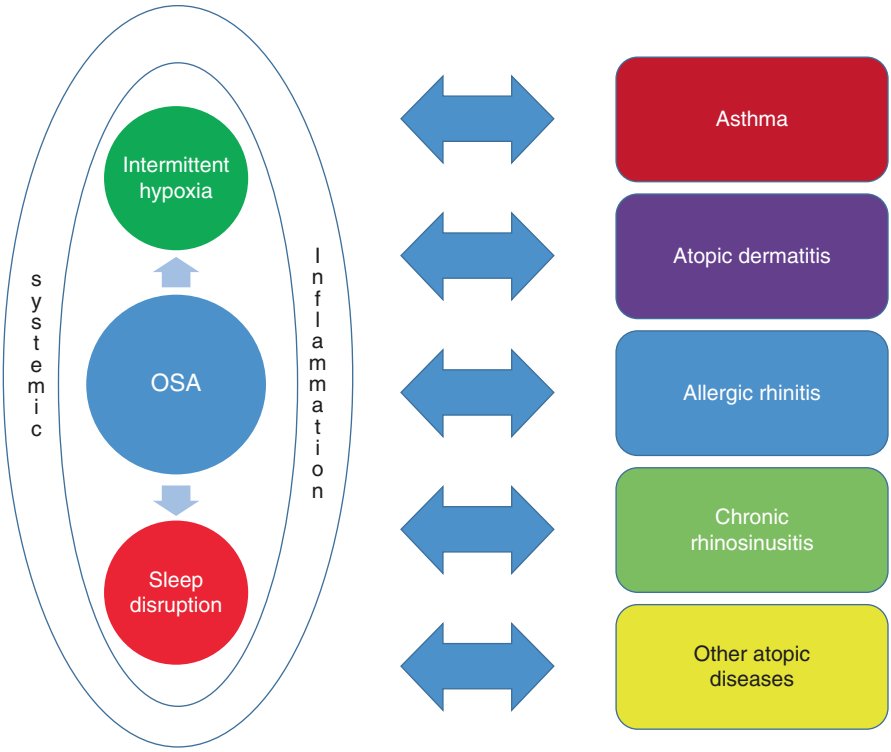


Fig. 1.1 Schematic of the reciprocal interactions between sleep and various atopic conditions that are covered in this book

The relationship between OSA and other atopic diseases such as allergic rhinitis and atopic dermatitis is covered in greater detail in the rest of this book and will thus only be briefly alluded to in this chapter (Fig. 1.1). In 2015, members of the Work Group on Rhinitis and Sleep-Disordered Breathing conducted a web-based survey to members of the American Academy of Allergy, Asthma & Immunology [40]. Eighty-two percent of respondents treated were both adults and children, while 9% treated just children. While taking into account the low response rate of just 7% to the survey with the ensuing possibility that responders may have self-selected on the basis of their level of interest in this clinical topic, it is still illuminating to see that the majority of respondents routinely asked about sleep problems, believed that sleep-disordered breathing was a problem for at least a substantial minority (10–30%) of their patients, and believed that medical therapy for upper airway inflammatory conditions could potentially help ameliorate sleep-related complaints. Of the respondents evaluating children with suspected OSA and adenotonsillar hypertrophy, 60% used anti-inflammatory medication as initial therapy, although most managed cases in collaboration with an otolaryngologist.

Obstructive Sleep Apnea and Autoimmune Disorders

It has been hypothesized that OSA leads to the development and worsening of autoimmune disorders via the pathways of intermittent hypoxia during sleep and sleep disruption per se as evidence by the increased arousals from sleep required to facilitate upper airway opening. The aforementioned factors lead to a chronic systemic inflammatory state and immunological changes which are postulated to contribute to the pathophysiology of these autoimmune diseases. Examples include the relationships between OSA and psoriasis, rheumatoid arthritis, and systemic lupus erythematosus.

OSA and Rheumatoid Arthritis

A bidirectional relationship exists between rheumatoid arthritis (RA) and OSA. A recent nationwide cohort study has revealed that patients with sleep disorders exhibited a 1.49-fold greater risk of developing RA compared with the comparison cohort when adjusted for covariates [41]. Conversely, a large population-based retrospective cohort study of 33,418 patients newly diagnosed with RA compared with 33,418 randomly selected controls showed an overall incidence rate of OSA that was 75% greater in the RA cohort than in the non-RA cohort, with an adjusted hazard ratio of 1.75 [42]. The pathophysiology by which RA can contribute to the development of OSA is better understood – RA can cause anatomical changes which result in OSA. For example, when RA affects the temporomandibular joint, destruction of this joint can lead to adult onset micrognathia or retrognathia, and the resultant anatomical narrowing of the oropharynx can result in OSA [43, 44]. Similarly, cervical spine instability secondary to RA can result in OSA: a study of RA patients with occipitocervical lesions showed that 79% had significant OSA and that a smaller atlantodental interval and shorter cervical lengths was associated with OSA [45]. Immobility due to painful arthritic hip or knee joints may predispose to weight gain which is another risk factor for OSA. Sleep problems such as poor sleep quality and sleep fragmentation are often reported in RA patients [46]. Sleep disturbances can exacerbate pain, and both are associated with poorer quality of life in these patients [47].

OSA and SLE

A large retrospective cohort study demonstrated that sleep disorders increased the risk of developing SLE with an overall adjusted hazard ratio of 2.20 [48]. SLE patients have been shown to have poorer sleep efficiency with increased arousals and decreased stage 3 and 4 sleep [49]. Poor sleep quality is common in patients with SLE and adversely affects their quality of life [50]. Contributing factors besides disease activity also include depression, SLE medications such as prednisolone, and fibromyalgia [50, 51].

OSA and Psoriasis

A large retrospective cohort study has shown that OSA is associated with an increased risk of developing psoriasis with a hazard ratio of 2.30 [52]. Psoriasis may also contribute to sleeping difficulties from associated depression or nighttime itching [53].

OSA and Cancer

Epidemiological studies have highlighted the association between OSA and cancer. The Wisconsin Sleep Cohort study showed that compared with control subjects, the adjusted relative hazard ratios of cancer mortality were 1.1 for mild SDB, 2.0 for moderate SDB, and 4.8 for severe SDB [54]. Similar findings were reported by a large multicenter Spanish cohort, though the difference was more significant in younger patients aged <65 years [55]. When overall cancer incidence was examined in the Spanish cohort, the severity of OSA as indicated by the number of respiratory events per hour of sleep was not associated per se with cancer incidence in the adjusted analyses, except for patients younger than 65 years. However, increasing severity of nocturnal hypoxia was associated with increased cancer incidence [56]. Of note, a database analysis in 1.7 million patients with OSA matched with 1.7 million of age-, gender-, co-morbidities, and local of residence controls also revealed that specific cancers were more likely in OSA, namely, pancreas, melanoma, lung, and kidney malignancies [57]. Intriguingly, in a pilot study of 18 patients with severe OSA, whole-genome expression of peripheral blood leucocytes was performed, and gene set enrichment analysis at baseline compared with post effective treatment with CPAP revealed a number of enriched gene sets, some of which were involved in neoplastic processes and were downregulated posttreatment [58].

In animal tumor models, mice exposed to sleep fragmentation (SF) had significantly larger and more invasive tumors than controls [59]. More tumor-associated macrophages (TAMs) were present in tumors from mice exposed to SF, and their distribution was closer to the tumor capsule as opposed to the tumor core as seen in the control mice. TAMs release growth factors, cytokines, inflammatory mediators, and proteolytic enzymes implicated in tumor growth and invasion and thus play a critical role in determining the tumor microenvironment. M1 macrophages exert antitumor properties, while M2 macrophages support tumor proliferation and invasion. The TAMs in the SF mice were predominantly M2 macrophages while expressing higher levels of TLR4. The more aggressive tumor phenotype was abrogated in TLR4 knockout mice, suggesting TLR4 signaling mediates SF-induced tumor progression. Further research is required to elucidate the role of OSA in this immunological context. Interestingly, reduced NADPH oxidase activity has been demonstrated within the solid tumor microenvironment of these mice, which may explain in part the increased tumor aggressiveness under SF conditions [60].

Animal tumor models exposed to intermittent hypoxia (IH) have also demonstrated increased tumor growth, invasiveness, and metastasis [61]. Similar to SF, IH appears to induce alterations in the host immune response such as a shift in macrophage polarity from M1 to M2, which results in the tumor's more aggressive phenotype [62]. IH may induce an imbalance in oxidation/reduction processes, resulting in the generation of excessive reactive oxygen species. It can also trigger an inflammatory response and modulate transcriptional factors such as hypoxia-inducible factors (HIFs) and NF-κB [63]. Increased tumor vascularization has been observed in IH mice which could be mediated by the upregulation of vascular endothelial

growth factor (VEGF) via HIFs. This increased vascularization could facilitate tumor cell migration into the circulation and thus metastasis.

SF and IH can both result in surges in sympathetic outflow and corresponding changes in systemic and local tissue catecholamine levels. β-Adrenergic signaling has been shown to increase macrophage infiltration into primary tumor parenchyma and their shift toward M2 macrophage differentiation [64]. It can also induce a metastatogenic tumor cell type by directly regulating gene expression and increasing migratory activity of tumor cells [65].

Severe OSA patients (adults) have been shown to have significantly reduced levels of circulating invariant natural killer T (iNKT) cells compared with patients with mild/moderate OSA and controls [66]. These levels increased following 12-month treatment of OSA with CPAP therapy. In vitro experiments on iNKT cell lines demonstrated increased apoptosis and impaired cytotoxicity when the cells were exposed to a 24 h period of hypoxia. As iNKT cells are another immune cell type which plays an important role in cancer immunity, these observations may be another contributing factor to the increased cancer risk reported in patients with OSA.

Conclusions

Sleep and the immune system are intricately linked. Many immune disorders may affect sleep, and reciprocally, sleep characteristics may affect the clinical course of these diseases via interactions with the immune system. Taking a thorough sleep history, addressing sleep hygiene and having systems in place to screen for and treat common sleep disorders such as OSA should be a prerequisite in the overall holistic care of patients. Certainly, the emerging evidence would suggest that greater awareness and improved management of sleep disorders in patients with associated diseases may improve disease outcomes.

And now, “to sleep, perchance to dream”…

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Overview of Basic Immunology

2

Barry J. Pelz and Joshua B. Wechsler

Every day, humans are exposed to environmental challenges from potential pathogens such as bacteria, viruses, and fungi. This exposure occurs in several sites throughout the body including the airway, skin, and gastrointestinal tract, as these are continuously interacting with the environment. Yet exposure often does not lead to infection or illness.

The immune system has evolved at multiple levels to defend against unwanted invaders. Although the human immune system is quite adept at these defenses, it can become dysfunctional and inappropriately respond to presumably harmless stimuli (e.g., atopic disease, celiac disease, or inflammatory bowel disease) or pathologically lose the ability to regulate cell proliferation (e.g., cancer). An intricate interplay of various specialized immune cells including T and B cells, regulatory cells, mast cells, basophils, neutrophils, natural killer cells, dendritic cells, macrophages, and structural cells underlies innate and adaptive immunity. While the innate immune system functions as an initial barrier to foreign agents, it also communicates with the adaptive immune system to develop a focused response to eliminate a pathogen and repair the tissue. Along with mucosal sites of immunity, specialized secondary lymphoid sites exist such as the draining lymph nodes, thymus, and spleen which coordinate adaptive immune function. An understanding of the basic components and function of the immune system is critical to understanding the development of chronic diseases of immune dysfunction. In this chapter, a basic overview of the functional components of the immune system is presented.

B. J. Pelz (✉)
Division of Asthma, Allergy, and Clinical Immunology, Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI, USA
e-mail: bpelz@mcw.edu

J. B. Wechsler
Division of Gastroenterology, Hepatology & Nutrition, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

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Table 2.1 Features of innate vs adaptive immunity

Features of innate and adaptive immunity		
Characteristic	Innate	Adaptive
Specificity	Non-specific; responds to patterns/motifs	Highly specific; responds to specific microbial and non-microbial antigens
Diversity	Limited; germ line encoded	Vast
Memory	None	Present
Response	Rapid (within hours)	Slower (within days)
Components	Structural barriers (epithelium) and innate immune cells (DCs, macrophages, neutrophils, mast cells, basophils, eosinophils, and innate lymphoid)	T and B lymphocytes, effector cells, and antibodies
Reactivity to self	None	None

Innate vs. Adaptive Immunity

The immune system comprises a complex network of anatomic sites, structures, and cells throughout the body that function to prevent, detect, and eliminate foreign, unwanted agents [1]. This is accomplished by two unique but interactive arms of immunity: the innate and adaptive immune systems. Innate immunity is considered to be a first line of defense against pathogens. It consists of physical, chemical, and biological barriers such as epithelial cells, cilia, mucous, and immunoglobulin A (IgA) which are in place before an infection occurs and poised to respond rapidly when needed (Table 2.1). Tissue-resident antigen-presenting cells function to detect antigen and process and present it to the adaptive immune system. This drives immune cell recruitment after toxic or infectious stimuli and stimulates the removal of foreign substances or infected cells. When aberrant, this can lead to chronic inflammatory diseases. Finally, the innate immune system can activate complement to target bacteria or facilitate removal of cellular debris or antibody complexes.

Innate responses are non-specific. They work quickly and without memory. This is unlike the adaptive immune system, which responds to stimuli more slowly with memory via cell-mediated or antibody-mediated (humoral) processes through the function of T and B cells (discussed in more detail later in this chapter). The adaptive immune response leads to a more stimuli- or insult-specific response. Importantly, adaptive immunity requires differentiation of "self" from "nonself." Both the innate and adaptive immune systems work hand in hand to find a balance to keep one healthy. The systems can become dysfunctional as is the case with autoimmune disease or primary immune deficiencies.

Innate Immunity

The role of the innate immune system is to provide an initial line of defense against pathogens, present antigen, and communicate with the adaptive immune system. While outer structural cells such as epithelial cells interface with the environment, sentinel (resident) cells such as mast cells, dendritic cells, and macrophages rapidly

respond to pathogenic insults that breach the epithelial barrier. These innate immune cells are derived from the common myeloid progenitor as are eosinophils, basophils, and neutrophils. These cells are recruited to enhance the innate defense and repair damaged or breached tissue. These cells also interact in sites of inflammation to rapidly halt pathogens from spreading.

Anatomic and Physical Barrier

Epithelial surfaces form physical barriers between host tissues and pathogens found in the external environment. These specialized surfaces are found in the areas of the body that interface with the outside world, namely, the skin and the mucosal lining of the respiratory, gastrointestinal, and genitourinary tracts. These surfaces are coated with specialized cells called epithelial cells which serve several functions. Physically, these cells serve a barrier function, as they form tight junctions with one another and thereby block the passage of microbes between the cells. Loss of the integrity of these epithelial tight junctions from a physical injury, wound, burn, or other insult can lead to an increased risk of infection. Keratinocytes, which comprise the outer layer of the skin, form keratin and block microbial penetration into deeper layers of the skin's surface. Mucous, a mucin-filled viscous material, is produced by the epithelial cells lining the respiratory, gastrointestinal, and genitourinary tracts. This viscous layer not only physically impairs microbial penetration into these tissues but also facilitates removal of the microbes by ciliary action in the respiratory tract and by peristalsis in the gastrointestinal tract.

In addition to their physical defenses, epithelial cells also serve an antimicrobial function, by producing defensins and cathelicidins. Defensins are small cationic proteins that are produced by epithelial cells and by certain lymphocytes, including neutrophils, natural killer cells, and cytotoxic T lymphocytes. These proteins have direct cytotoxic effects on microbes and also serve to activate other immune cells involved in the inflammatory response. Cathelicidins are proteins that are produced by neutrophils and by the various epithelial cells lining the skin, respiratory tract, and gastrointestinal tract. Cathelicidins also serve an antimicrobial role, as they too have toxic effects on microbes and activate various leukocytes and other immune cells to eradicate a potential invader.

A third protective function of the epithelial barrier is aided by the presence of intraepithelial T lymphocytes. These lymphocytes are found in the skin and in the mucosal epithelia. While there are various subsets of these intraepithelial T lymphocytes, they all are believed to recognize a small number of common microbial structures such as PAMPs (pathogen-associated molecular patterns) and to aid in direct killing of microbes and infected cells.

Dendritic Cells

Dendritic cells are specialized cells that are constitutively present in the epithelia and most body tissues [2]. They have long membranous projections and phagocytic capabilities that allow them to sample microbes from the lumen, uptake the antigen, and

present the antigen to circulating lymphocytes. Dendritic cells are the most important antigen-presenting cell for activating naïve T lymphocytes, and therefore they play a major role in connecting the innate and adaptive immune systems. The majority of dendritic cells are conventional dendritic cells. Once activated by antigen, conventional dendritic cells migrate to the lymph nodes and present microbial antigen to naïve T cells for activation. By these same mechanisms, dendritic cells play a major role in allergic disease, as they can uptake allergens detected in the epithelial surfaces and present them to naïve T cells. A subtype of dendritic cells called plasmacytoid dendritic cells are adept at recognizing viral nucleic acids and are thus heavily involved in antiviral defenses. They produce antiviral cytokines called type I interferons to sound the alarm against a viral invader. In the skin, specialized immature dendritic cells called Langerhans cells are adept at trapping microbes and transporting these proteins to the lymph nodes. Because of their abundant, resident nature and expert ability to present antigen, dendritic cells are an important part of innate immunity and a key connection between the innate and adaptive immune systems.

Monocytes/Macrophages

Macrophages are important cells involved in the innate immune system's early response to infection. Derived from the monocyte/dendritic cell precursor in the bone marrow, these cells circulate in the blood before maturing and becoming activated in various tissues. The monocyte is an immature cell that emerges from the bone marrow precursor and circulates in the bloodstream. It is a mononuclear cell with a cytoplasm full of granules, lysosomes, and phagocytic vacuoles. When these cells enter tissues, they mature into macrophages. Macrophages in different body tissues are designated by specific names. The macrophages of the central nervous system are known as microglial cells. Those in the liver are called Kupffer cells, and those in the respiratory tissues are called alveolar macrophages.

Macrophages have numerous functions. One of their main roles is to ingest and kill microbes, which they accomplish through a combination of phagocytosis, generation of reactive oxygen species, and proteolytic degradation. Macrophages ingest dead or dying cells to help with tissue repair, and in addition to this phagocytic role, they also aid in tissue repair by stimulating the formation of new blood vessels (angiogenesis) and new collagen matrix proteins (fibrosis). Another very important function of macrophages is the secretion of cytokines to signal and instruct other cells in coordinating the immune response. Lastly, macrophages can serve as antigen-presenting cells (APCs) that display and present antigens to T lymphocytes for further activation and immune responses.

Neutrophils

Neutrophils are the most abundant of the circulating white blood cells and are arguably the most important cell in the innate immune response [3]. These cells contain multi-lobed or multi-segmented nuclei and are thus sometimes referred to

as polymorphonuclear lymphocytes or segmented neutrophils. Their nuclei are filled with various granules. Unlike other circulating granulocytes, the granules of neutrophils do not stain strongly with hematoxylin or eosin. Instead, these granules contain various substances such as lysozyme, collagenase, elastase, defensins, and cathelicidins, all of which are extremely important in host defense.

In most cases of infection or tissue injury, neutrophils are the first leukocytes recruited to the affected site. After being recruited through a multistep process that is dependent on the detection of selectin, integrin, and various site-specific chemokines, neutrophils migrate to the site of infection within a few hours of microbial entry. Once neutrophils enter inflammatory sites, they perform various effector functions. Neutrophils in the tissue will phagocytose microbes and expose them to high concentrations of bactericidal substances in the phagocytic vacuole. The microbicidal mechanisms they use include the generation of reactive oxygen species (the oxidative burst) and exposure to proteolytic enzymes. Both function to destroy microbes, although strongly activated neutrophils can also damage host tissue as a result of the release of these products. Lastly, neutrophils produce signals that attract additional neutrophils as well as macrophages and T cells to the site of injury to help orchestrate their activity. Defects in neutrophil production and function can result in diseases such as severe congenital neutropenia, chronic granulomatous disease, or leukocyte adhesion deficiency. In general, these diseases are characterized by the potential for recurrent and severe infections of bacterial and fungal origin. Thus, clearly the neutrophil is an important player in the immune response.

Mast Cells, Basophils, and Eosinophils

Mast cells, basophils, and eosinophils are the main effector cells involved in allergic hypersensitivity reactions, and they also play important roles in the innate and adaptive immune systems [4]. Linked by their presence of cytoplasmic granules and their expression of similar receptors and cytokines, these cells differ in their trafficking, activation, and effector functions.

Mast Cells

Mast cells are bone marrow-derived, tissue-based inflammatory cells. Mast cell precursors arise in the bone marrow, circulate in the blood, and then home to the tissues where they mature. Once mature, mast cells reside in healthy tissues where they are primarily found near blood vessels, nerve cells, or epithelial surfaces. Mature human mast cells are subdivided into two major categories, mast cell tryptase predominant (MC_T) or mast cell tryptase and chymase predominant (MC_{TC}). All mast cells express the receptor for stem cell factor, c-kit (CD117), as well as the high-affinity IgE receptor, FCεR1. In addition, mast cells express various other receptors depending on their location and state of activation. These can include the receptors for IgG, C3a, and C5a as well as IL-3R, IL-4R, IL-5R, GM-CSFR, CCR3, CCR5, CXCR2, and toll-like receptors (TLRs).

Mast cells are famously known to be activated through the FCεR1 receptor, forming the basis for anaphylaxis as well as allergic rhinitis and allergic asthma. Antigen cross-links IgE bound to this high-affinity receptor driving degranulation and mediator production/release. Mast cells are also activated by complement proteins, neuropeptides, and microbial products. They thereby play a role in defense against helminths. They are also thought to function in homeostasis, wound healing, and innate and adaptive immunity based on animal studies.

Upon activation, mast cells release various mediators. These include preformed mediators, newly synthesized lipid mediators, and various cytokines and chemokines with late-phase actions. The preformed mediators present in mast cell granules include histamine, tryptase, chymase, and proteoglycans, all of which get released through fusion with the plasma membrane within minutes of mast cell activation. Histamine facilitates the development of edema, while serine proteases and cytokines can drive inflammation. Mast cells also signal with nerves driving excitation potentials. In addition, mast cells promote fibrogenesis through activation of myofibroblasts.

Basophils

Basophils are structurally and functionally similar to mast cells, but they comprise a distinct lineage with unique characteristics. Basophils are derived from a bone marrow precursor. They differentiate and mature in the bone marrow and then circulate in the periphery, where they constitute less than 1% of circulating lymphocytes. Similar to mast cells, basophils express FCεR1 as well as receptors for IgG, C3a, and C5a. Basophils bind IgE and can be activated by antigen cross-linking of IgE receptors. Upon activation, basophils rapidly secrete Th2 cytokines, including IL-4 and IL-13 (in contrast to the mast cell which tends to produce large amounts of IL-5 and IL-13). Basophils then, in a manner similar to mast cells, secrete various mediators from their granules. These again include preformed mediators, newly synthesized lipid mediators, and various cytokines and chemokines. Basophils produce histamine and tryptase, though the amount of tryptase produced is less than that produced by the mast cell. The precise role of basophils in homeostasis, host defense, and allergic responses is not entirely understood.

Eosinophils

Eosinophils are a third bone marrow-derived cell of the granulocyte lineage. These cells get their name from their strong proclivity for the acidic stain eosin. The eosinophil is laden with potent basic granules which contain enzymes that are harmful to helminths and to host tissues. IL-3, IL-5, and GM-CSF are all important in promoting the development of eosinophils from the hematopoietic progenitor cell. While some eosinophils are normally present in the peripheral tissues, particularly in the mucosal lining of the respiratory, gastrointestinal, and genitourinary tracts, the

production of IL-5 from allergic inflammation or helminth infection leads to additional release of eosinophils from the bone marrow. Eotaxin is an important chemotactic factor that can lead to the release of eosinophils and eosinophil precursors from the bone marrow as well as to the trafficking of eosinophils to specific mucosal tissues.

While there is no consensus on the predominant pathway for eosinophil activation, activated eosinophils release potent pro-inflammatory mediators such as major basic protein, eosinophil-derived neurotoxin, and eosinophil cationic protein. Eosinophils are thought to play a role in tissue homeostasis and healing; however, an increase in peripheral blood- and tissue-specific eosinophil numbers occurs in a number of pathologic conditions, including allergic disease, drug hypersensitivity reactions, parasitic infection, connective tissue disorders, and hypereosinophilic syndromes (HES). Eosinophilia also has been a noted feature of some primary immunodeficiencies, including Omenn syndrome and Hyper-IgE syndrome. Viral and bacterial infections, in contrast, typically lead to an acute and transient eosinopenia.

Innate Lymphoid Cells

While dendritic cells, monocytes, macrophages, and granulocytes have been appreciated for decades, more recent discoveries in the last decade have identified innate lymphoid cells (ILCs) as a distinct part of the innate immune system [5]. These cells, derived from the common lymphoid progenitor, are present in lymphoid and nonlymphoid tissue. They respond to various stimuli including neuropeptides, hormones, cytokines, and alarmins. They appear to play an intricate role in orchestrating the responses of the innate and adaptive immune systems, as various functions are beginning to be described. There are now three distinct groups of ILCs: group 1 (ILC1), group 2 (ILC2), and group 3 (ILC3). These groups are defined in large part by the cytokines that they produce, and they are similar to Th1, Th2, and Th17 cells, respectively, in terms of their cytokine production. We anticipate that new insights about how these cells are involved in health and disease will continue to emerge in the coming years.

Innate Immune Response to Infection

Now that we have introduced the major cells of the innate immune system, it is useful to summarize the principles of the innate immune response to infection. Once a microbe breaches the physical defenses of the body, it encounters the cells of the innate immune system, where the initial immune response begins. This initial response involves inflammation and the generation of antiviral defenses. We discuss each of these components in more detail in the following paragraphs [6, 7].

Inflammation involves the recruitment of leukocytes and plasma proteins, the accumulation of these cells and proteins in the tissues, and their activation to destroy

the invading microbe. Inflammation is primarily carried out by phagocytes, neutrophils, and macrophages. The recruitment of these cells is mediated by cytokine secretion from dendritic cells, macrophages, and neutrophils. The cellular responses are then carried out by dendritic cells, macrophages, and neutrophils.

There are numerous aspects that comprise the host immune system's antiviral defense. Natural killer cells (NK cells) can kill virus-infected cells. The host itself can try to resist the invasion of viral proteins by recognizing them as foreign or dangerous. However, many pathogens have evolved mechanisms to avoid detection by the human immune system. Once a pathogen has breached the initial immune defense system, the pathogen may encounter various circulating cells and proteins in the host's bloodstream. The complement system involves circulating proteins of the immune system and can be activated by viral pathogens. Numerous other circulating proteins, such as defensins, mannose-binding lectin, and LPS-binding protein, are also capable of activating an initial immune response.

The innate immune system relies upon a limited number of recognition receptors to generate a rapid and protective response. In order to compensate for the need to recognize only a few patterns, the receptors of the innate immune system are specific for highly conserved motifs which are common to multiple groups of pathogens.

The innate immune system uses three main strategies to recognize that a response may be warranted. One strategy involves detecting elements of microbial nonself protein, utilizing germ line-encoded receptors such as toll-like receptors or NOD-like receptors to recognize motifs that are made of highly conserved structures in a variety of microbes. These receptors have been given the name pattern recognition receptors (PRRs), and the microbial structures that they recognize have been called pathogen-associated molecular patterns (PAMPs). A second strategy used by the innate immune system is to detect typical consequences of cell infection or injury, or the so-called damage-associated molecular patterns (DAMPs). DAMPs are molecules that are released or upregulated during tissue damage and/or cell lysis. These include heat-shock proteins, uric acid, and other alarmins and can be detected by NOD-like receptors (NLRs) and others. In the third strategy, the innate immune system can detect cells that are missing markers of self. In these responses, the immune system sounds the alarm when molecules that are normally present in healthy cells are no longer present in damaged or diseased cells. An example of this strategy is shown by NK cells which attack damaged cells that have downregulated their self MHC class I proteins and therefore no longer have a marker of self on their surface.

Adaptive Immunity

The adaptive immune system is responsible for a more precise but delayed response to specific stimuli. Adaptive immunity is more specific and more diverse, allowing it to respond to a range of stimuli with greater specificity. Adaptive immunity also has memory, allowing it to create secondary adaptive immune responses which are more robust than the body's initial primary response.

Features of Adaptive Immunity

The adaptive immune response can be divided into two arms, humoral immunity and cell-mediated immunity. These branches are characterized by the cells which carry out their functions and the types of microbes they target. Humoral immunity is mediated by B lymphocytes (or B cells). B cells secrete antibodies and target extracellular pathogens and their toxins. The antibodies that B cells secrete recognize microbial pathogens, coat them, neutralize them, and target them for elimination by various other players in the immune system. Cell-mediated immunity or cellular immunity is mediated by T lymphocytes (T cells) and is active against intracellular pathogens such as viruses and some bacteria. Cell-mediated immunity aims to kill infected cells or promote the destruction of microbes that are residing in phagocytes.

All adaptive immune responses, including humoral and cellular immunity, have a number of cardinal features in common. First, the immune responses are specific. The adaptive immune responses are predicated upon the antigen-specific receptors on the surfaces of T and B lymphocytes. In contrast to the germ line-encoded recognition receptors found in innate immunity, T and B lymphocytes undergo a detailed maturation process that involves rearrangement of germ line elements to form newly made and highly specialized T- and B-cell receptors. Each of these receptors has a unique specificity to pathogens, allowing the response to be precisely targeted. The mechanisms that enable nearly infinite rearrangement possibilities lead to yet another feature of the adaptive response, diversity. The total repertoire that the adaptive immune system can respond to is extremely diverse. Lymphocytes that are specific to a specific pathogen undergo clonal expansion, whereby millions of multiples of a specific cell and its receptor are expanded in response to the pathogen. This contributes to the delay in the adaptive immune response but at the same time underlies its ability to have a targeted and specific response. A fourth feature of the adaptive immune system is memory. Exposure to a pathogen often leads to the formation of long-lived memory cells which are capable of a more rapid and more robust response upon subsequent exposures. Lastly, the adaptive immune response is characterized by contraction and homeostasis. After a response has occurred, the immune system returns to its resting basal state.

T and B Lymphocytes Are Key Components of Adaptive Immunity

The important cell types of the adaptive immune response arise from the common lymphoid progenitor, a hematopoietic stem cell in the bone marrow. The common lymphoid progenitor gives rise to the T lymphocytes, which mature in the thymus, and the B lymphocytes, which mature in the bone marrow. Once the lymphocytes have matured, these immunologically naïve cells can then emerge into the circulation and lymphatic system.

T Cells

T lymphocytes are involved in adaptive immune responses and are critical for fighting intracellular pathogens and activating B cells against antigen. T lymphocytes consist of functionally diverse populations, including the helper T cells, cytotoxic (killer) T cells, and regulatory T cells. These distinct populations have different effector functions. Activated CD4 helper T cells proliferate and differentiate into effector cells who function largely through the secretion of cytokines in an effort to enhance T- and B-cell responses. Some secrete cytokines that further recruit or lead to specific classes of antibody production or recruit other cell types (such as IL-5 that stimulates eosinophilic recruitment). Activated CD8 lymphocytes proliferate and differentiate into cytotoxic lymphocytes that kill infected cells. Still other T lymphocytes regulate immune responses through various regulatory functions carried out by T regulatory cells (Tregs). Low numbers and dysregulation of T regulatory cells have been associated with many allergic diseases.

A key component of T cells is the T-cell receptor (TCR), which recognizes antigens as peptide fragments bound to major histocompatibility complex (MHC). Major differences occur in the peptide-binding grooves of MHC class I (MHCI) and MHC class II (MHCII) which explains why MHCI-bound peptides present to CD8 T cells and MHCII- receptors present to CD4 helper cells. T cells are often differentiated by CD4, a TCR co-receptor that binds MHCII on the surface of T-helpers cells, and CD8, a co-receptor for the TCR that binds MHCI found on cytotoxic T lymphocytes.

Notably, there are specific types of CD4 cells; T-helper type 1 and type 2 are the most well recognized (Fig. 2.1 for details). T-helper cell type 1 (or Th1) responses are directed at pathogens that play a big role in macrophage activation. A prominent role exists for cytokines such as IFN and IL-8, with neutrophilic inflammation being a common finding. HIV is a notable example of defective Th1 immunity. The T-helper type 2 system is thought to evolutionarily have a critical role in fighting helminths and is characterized by mast cell activation and eosinophilia. Dysregulated Th2 immunity is commonly seen in allergic diseases with a prominent role for IL-4, IL-5, and IL-13. Classic examples are atopic dermatitis (eczema), asthma, and eosinophilic gastrointestinal diseases. Less appreciated T-helper responses are Th22, Th9, and Th17. The Th22 response is similar to Th2, but is also associated with cytokine IL-22, and is an important cell type which is present in atopic dermatitis. The T-helper type 9 response appears to play a role in intestinal allergic diseases and is mast cell associated. The Th17 response is similar to Th1 and facilitates killing of extracellular bacteria and fungi by neutrophil recruitment and activation. Key cytokines are IL-17 and IL-22. Crohn's disease is thought to have aspects of this type of immune response. In addition to pro-inflammatory T cells, there are regulatory T cells that play a role. These T regulatory cells are commonly identified by FOXP3 and are important in maintaining tolerance by suppressing the development of an aberrant inflammatory response. They are also important in cancer surveillance.

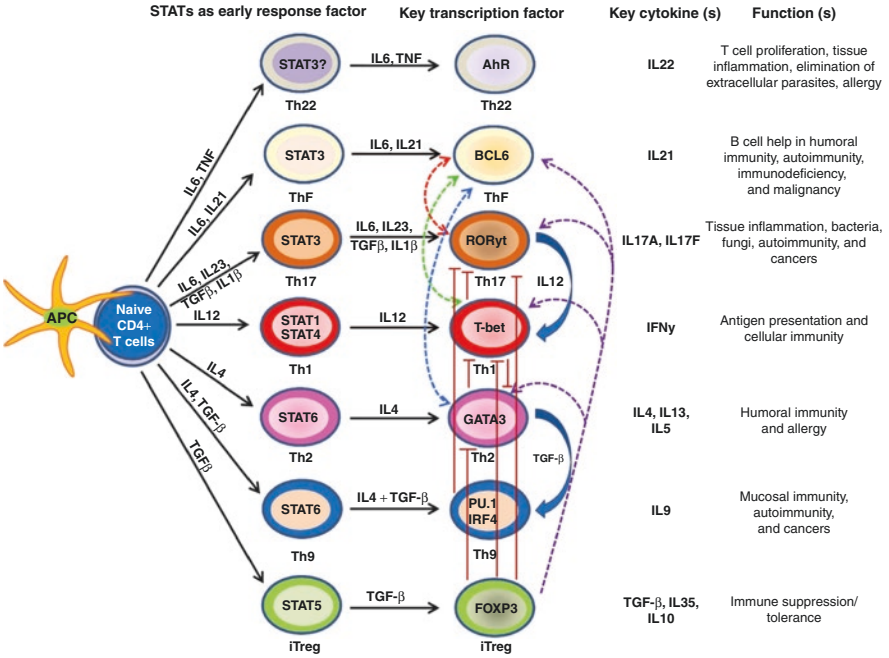


Fig. 2.1 CD4+ T-helper cell subsets and their plasticity. Depending on the nature of antigen stimulation signal received from APCs, naive CD4+ T cells differentiate into distinct effector T-helper and regulatory T-cell subsets, which are characterized by expression of lineage-specific transcriptional regulators, cell surface markers, and secretion of key cytokines. Due to plasticity, differentiated effector CD4+ T cells can convert from one cell type into another. Uncontrolled regulation of lineage specification and commitment can result in development of inflammatory and allergic diseases. (From Tripathi and Lahesmaa [8], with permission)

Critical to immunity are CD8 cells, otherwise known as cytotoxic T cells, lymphocytes, or killer T cells. These cells are capable of identifying infected or damaged cells that need to be removed. Unlike CD4 cells which bind MHCII, CD8 cells bind MHCI along with CD80 or CD86 (via CD28). CD8 cells can develop memory for reactivation on second exposure. The cells are characterized by the release of cytotoxic perforins and granzymes or activation of FAS. Both mechanisms drive cell death.

B Cells

Humoral immunity is carried out by the secretion of antibodies, which is the main job of the B-cell lineage. Antibody secretion can be stimulated by either multivalent, carbohydrate antigens or by protein antigens. Carbohydrate antigens stimulate B-cell production of antibodies without T-cell help (T-independent antigens), while protein antigens are presented by B cells to helper T cells to result in T-dependent antibody

production. The T-dependent antibody production results in antibodies with higher affinity and more diverse functions than T-independent antibodies. Thus, T-dependent antibodies are the most effective mediators of humoral immunity.

Resting mature B cells in the peripheral lymphoid tissues are activated by antigen. This stimulates B cells to proliferate rapidly and generate a robust immune response. Some of the B cells that expand undergo class switching to make various classes of antibodies (including IgM, IgA, IgG, and IgE). Activated B cells with the strongest affinity for the antigen assume control of the immune response through a process known as affinity maturation.

Under the influence of cell signals and cytokine receptors, some B cells develop into long-lived plasma cells and memory cells which live for many years and can provide an immune response on subsequent exposure to the same antigen. Primary immune responses occur when naïve B cells respond to an antigen. In contrast, a secondary immune response occurs when expanded clones of memory B cells are stimulated. As a result, secondary immune responses are more rapid and more powerful (due to the quick production of larger numbers of antibodies) than primary responses.

When a B cell is activated, it will be influenced to produce certain antibodies depending on the antigenic trigger, the cellular signals, the cytokines that are present, and the overall immune milieu. IgM antibodies bind to bacteria, activate the complement system, and induce phagocytosis of the opsonized bacteria. The response to polysaccharide antigens is primarily characterized by IgM. In contrast, most viruses and bacteria lead to the production of IgG antibodies. These antibodies work to prevent the pathogen from entering the host cells. IgG also helps to promote phagocytosis of the pathogen by macrophages. IgE is the main antibody response involved in defense against helminths and parasites. As mentioned in the eosinophil and mast cell sections, IgE is also the main antibody involved in immediate hypersensitivity reactions. IgA is the antibody class that is most efficiently transferred from epithelial interfaces into mucous. Thus, many B cells in mucosal tissues class switch to form IgA upon activation. As with T-cell activation and signaling, there are numerous important cell surface molecules, cytokines, signaling interactions, and pathways that are important in B-cell class switching and B-cell function. Many of these interactions have been well described but are beyond the scope of our introductory chapter.

Activation of Adaptive Immune Responses

Activation of antigen-presenting cells is an initial step for induction of adaptive immunity. Through interaction with naïve T cells, antigen-specific T cells arise. Clonal selection of lymphocytes is a central principle, involving CDR3, with hypermutation of V(D)J. Each developing lymphocyte generates a unique receptor by rearranging its receptor gene segment. Antigen-specific T cells interact with B cells to generate antibodies, although adaptive responses can also be primarily cellular when warranted. The development of an immune-specific response can lead to immunologic memory, which can form with either T cells or B cells.

Immune-Privileged Tissues

Immune-privileged sites are tissues that are insulated from immune responses. These include the anterior chamber of the eye, the brain, and the testis. These tissues have evolved to be protected from immune response, to a variable degree, due to a high risk of lethal organ dysfunction or reproductive failure in the event of immune activation. These sites instead rely on tight junctions within endothelial cells, immunosuppressive cytokines, and expression of cell surface molecules that limit inflammatory cells. Tight junctions and an avascular cornea limit access of the adaptive immune system to the eye. There are instead several soluble factors such as anti-inflammatory and immunosuppressive neuropeptides present in the ocular tissue. In the brain, similar tight junctions create a so-called blood-brain barrier to prevent inflammation and neuronal death. The brain is rich in resident macrophages, called microglia, which become activated in response to tissue damage or infections in the brain, although more recent evidence of latent JC virus activation in patients who are immunosuppressed with monoclonal antibodies suggests some T-cell and monocyte trafficking as well. The testes' blood-tissue barrier both limits inflammation which may impair fertility and also prevents autoimmunity against self-antigens that are expressed at different times in the life cycle (i.e., spermatogenesis at puberty). Similarly, the maternal-fetal dyad becomes an immune-privileged site during pregnancy, as local mechanisms at the site underlie maternal immunologic tolerance to the developing fetus, despite the fetus expressing allogeneic paternal antigens.

Conclusion

The world is full of potential invading pathogens and toxins that regularly challenge the human immune system. Fortunately, the immune response has evolved to constitute a complex network of structures and cells that act in concert to defend against pathogens. The innate immune system utilizes physical barriers and rapid, germ line-encoded cells and recognition systems to create a first line of defense. This system then communicates with the more advanced and precise adaptive immune system, whose effector T and B lymphocytes can carry out the remaining immunologic tasks in a specific and robust manner, which is further characterized by the generation of immunologic memory. While the innate and adaptive immune systems are often discussed as separate entities, the two are truly intertwined. Many of the adaptive immune responses build on the foundation of the innate immune responses, as demonstrated by T and B lymphocytes needing antigen-presenting cells in order to become activated. Similarly, the functions of the innate immune system are greatly enhanced by the presence of the adaptive immune system, as demonstrated by the fact that neutrophils are more efficient at phagocytosis of microbes that have been coated with antibody secreted by activated B cells. Thus, the innate and adaptive immune systems work in concert to maintain health and fight off disease. The immune system has a tremendous role in both health and disease, and, as we will see in the remainder of this book, the immune system underlies numerous conditions related to allergy, sleep, and the disorders shared therein.

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Overview and Understanding of Basic Circadian Physiology

3

Sabra M. Abbott and Phyllis C. Zee

With the regular rotation of the earth on its axis, we live in a 24-hour environment, with daily patterns of light and darkness. Nearly all organisms studied have developed mechanisms to adapt to these daily, or circadian, rhythms of the environment by developing their own endogenous timekeeping mechanisms. The earliest observations that these rhythms appeared to be intrinsic to the organism, rather than simply a response to the environmental light/dark patterns, came from studies in plants. Jean-Jacques d'Ortous de Mairan observed that the *Mimosa* plant would open its leaves during the day and close them at night. These movements persisted, even if the plant were placed in constant darkness, implying that the plant had a means of sensing time, independent of exposure to light. Similar observations were also later made in both insects and mammals [1].

Regulation of Circadian Timing in Mammals

In mammals, lesioning studies of the rat hypothalamus demonstrated that the primary coordinator of these circadian rhythms is located in the suprachiasmatic nucleus (SCN). If rats are placed in an environment of constant darkness, free from

S. M. Abbott
Department of Neurology, Northwestern University, Chicago, IL, USA

P. C. Zee (✉)
Department of Neurology, Northwestern Medicine Feinberg School of Medicine, Chicago, IL, USA
e-mail: p-zee@northwestern.edu

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external time cues, elimination of this region abolished the previously observed daily rhythm of drinking behavior [2]. Similar results were found in hamsters, when looking at the rhythmic output of activity [3] or core body temperature [4]. It is also possible to remove the isolated SCN from the rat brain and measure the neuronal firing rate in vitro, which demonstrates a rhythmic daily peak in activity [5]. Interestingly, in hamsters it was demonstrated that these rhythms could be restored by placing SCN tissue from a rhythmic hamster within the lesioned hypothalamus [6] and the restored rhythm matches that of the donor [7]. Also, the SCN can be removed from the animal, and immortalized cell lines can be created that show persistent rhythmic activity in culture [8]. Co-culturing SCN neurons with fibroblasts can transmit this rhythmicity to nonrhythmic cells; however unlike SCN cells, rhythmicity in the fibroblast cells does not persist if the SCN signals are removed [9]. Overall this supports that idea that the SCN is able to independently sustain rhythmicity and can then transmit this rhythmicity to other cells, through diffusible factors.

The SCN is a set of paired nuclei, located in the hypothalamus, directly dorsal to the optic chiasm. Neuroanatomically it consists of a ventrolateral core containing vasoactive intestinal peptide (VIP) and dorsomedial shell containing primarily arginine vasopressin (AVP) [10]. The neurons in the shell appear to be intrinsically rhythmic and are more active during the day [11], while the neurons in the core tend to be more active at night but are thought to maintain this rhythmicity due to inputs from the AVP shell neurons [12]. As will be discussed later in this chapter, signals acting to reset the clock work primarily through interactions with the ventrolateral core of the SCN.

This intrinsic rhythm of the SCN neurons is regulated at a genetic level by a complex transcription-translation feedback loop. The first clock gene, *Period*, was identified in drosophila; [13] however homologs were later identified in mammals. At its core, the mammalian molecular clock consists of two positive elements, the genes *Clock* and *Bmal1*, and two negative elements, the genes *Period* and *Cryptochrome*. The proteins CLOCK and BMAL1 dimerize and activate the transcription of *Period* and *Cryptochrome*. The PER and CRY proteins dimerize and then feedback and inhibit transcription of CLOCK and BMAL1. Additional factors can modulate this core transcription-translation feedback loop, including casein kinase 1ε, which helps stabilize the PER/CRY dimer; ROR and REV-ERBα which regulate transcription of *Bmal1*; and DEC1 and DEC2, which regulate *Per* transcription [14]. Overall the full transcription-translation feedback loop takes ~24 hours to complete, and the precise timing of this determines the endogenous period of the individual organism. See Fig. 3.1 for details.

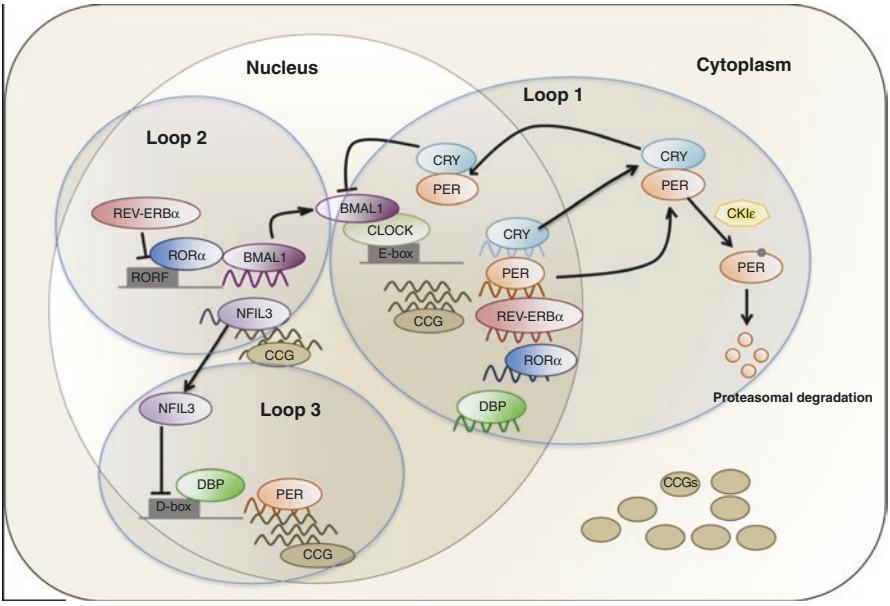


Fig. 3.1 Diagram of the molecular circadian clock. The molecular clock consists of at least three interlocking feedback loops. Loop 1 consists of the core clock proteins BMAL1 and CLOCK binding to E-box elements within the genes encoding the repressor proteins PER, CRY, REV-ERBa RORa, and DBP. After a period of time, PER and CRY can translocate back into the nucleus and repress their own expression by interfering with the BMAL1/CLOCK complex on the gene promoter. The expression of these proteins is regulated further by posttranslational modifications such as phosphorylation of PER by CKIε, which marks it for proteosomal degradation. Loop 2 consists of the alternate regulation by REV-ERBa and RORa on RORE promoter elements, which includes Bmal1 and Nfil3. Loop 3 consists of the alternate regulation by NFIL3 and DBP on D box promoter elements. The clock products from each of these loops can shuttle back to the nucleus and either repress or reactivate these loops. The transcription factors within each of these loops can also regulate clock-controlled genes (CCGs). These are genes that have a circadian profile of expression but do not feedback to affect the core molecular clock. If some of these CCGs are themselves transcription factors, they may confer a circadian profile of expression on their target genes. Therefore, the core clock components and CCGs have the capacity to regulate transcription of a wide variety of cellular programs that is independent of their function within the molecular clock (From Curtis et al. [70], with permission)

Circadian Output Signals

The output of the SCN can be reflected in the circadian timing of most physiological processes throughout the brain and body (Fig. 3.2). Perhaps the most readily appreciated of those rhythms is the daily cycle of rest and activity. While there are

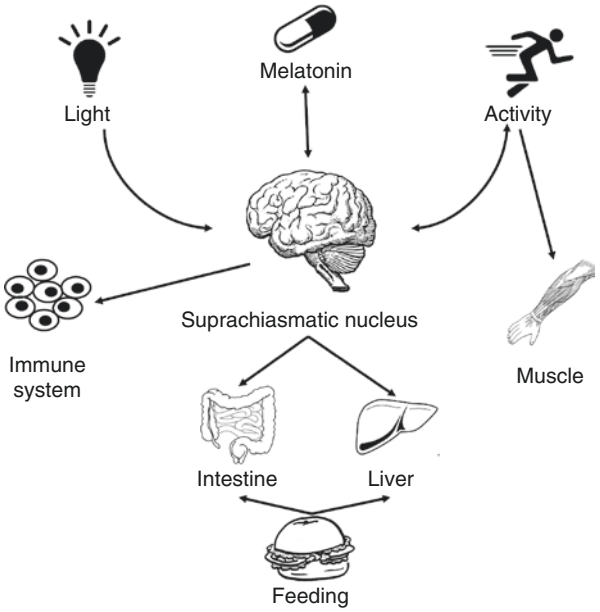


Fig. 3.2 Diagram of the circadian system. The primary circadian pacemaker is the suprachiasmatic nucleus (SCN), located in the brain. It provides timing signals to peripheral clocks throughout the body, including the immune system, intestine, liver, and muscle. Timing of the SCN can be regulated by inputs from the environment, including light and melatonin, while activity and the timing of feeding can indirectly feed back to the SCN, through influences on the peripheral clocks

certainly many behavioral factors that contribute to the self-selected timing of rest and activity, the circadian system regulates the optimal time for sleep and wake, along with the timing of many other important physiological functions, including feeding behaviors, core body temperature, and endocrine hormone release.

Individual SCN cells, when placed in dispersed-cell culture, exhibit rhythmic firing rates; however each cell has a slightly different circadian period. Interestingly, traditional communication through action potentials and synapses does not appear to be necessary for maintaining this rhythmicity [15]. There is evidence that one means by which SCN cells communicate with each other is through gap junctions [16] and that these connections are necessary for electrically synchronizing the SCN [17]. However, it was more recently demonstrated that mice lacking the connexin-36 protein that is necessary for forming these gap junctions and electrically coupling the SCN neurons still exhibit synchronized core clock gene expression [18]. Synchronization of the core clock genes is thought to be mediated by communication with the neurotransmitters GABA and VIP [19, 20].

One of the primary means by which the SCN communicates with the rest of the body is through the release of local diffusible factors, which influence areas along the ventricular system. These factors include the previously mentioned AVP, prokineticin 2 (PK2), transforming growth factor alpha (TGF-α), and cardiotrophic-like cytokine (CLC) [21]. In rodents AVP exhibits rhythmic patterns of release, with higher levels in the morning than at night [22], which appear to be stimulated by CLOCK/BMAL1 and suppressed by PER/CRY [23]. Rhythmic AVP release appears to in turn regulate rhythmic patterns of cortisol, luteinizing hormone (LH) [24], and gonadotropin-releasing hormone (GnRH) [25]. PK2 [26], TGF-α [27], and CLC [28] are all expressed rhythmically and inhibit locomotor activity when infused into

the third ventricle, providing a potential mechanism by which the SCN may regulate rest/activity patterns. Interestingly, while TGF-α inhibits rhythmic behaviors, including feeding and rest-activity, it has no influence on the rhythmic pattern of melatonin release [29]. PK2, on the other hand, appears to influence rest-activity, core body temperature, feeding behaviors, and the patterns of corticosterone and glucose release [30].

The primary neurological outputs of the SCN are to other regions of the hypothalamus and thalamus, including the subparaventricular zone (SPV), paraventricular nucleus (PVN), and dorsomedial hypothalamus (DMH) [21]. Projections to the SPV appear to be important for regulation of daily rest/activity patterns [31]. In addition, the dorsal SPV appears to be important for the circadian regulation of body temperature [32], while the preoptic area is more important for the homeostatic regulation of temperature. Projections to the PVN appear to be key for the circadian regulation of autonomic function. Projections from the PVN to the dorsal motor nucleus of the vagus nerve provide parasympathetic outputs, while projections from the PVN to the intermediolateral (IML) cell column of the spinal cord and then to the superior cervical sympathetic ganglia provide sympathetic output [33]. One of the primary autonomic output signals of the SCN is the rhythmic pattern of melatonin release from the pineal gland. This results from coordinated projections from the DMH to the IML in the cervical spinal cord, to the sympathetic ganglia, back to the pineal gland. Melatonin release typically is high at night and low during the day. While melatonin production is suppressed by light, daytime levels also remain low under constant dim-light conditions, providing evidence that this is also an endogenously regulated process [34].

Regulation of sleep-wake behavior appears to be through projections to the DMH, which in turn projects to the wake-promoting lateral hypothalamus (LH) and locus coeruleus (LC) and the sleep-promoting ventrolateral preoptic area (VLPO) [35]. Projections to the DMH also appear to be important for regulating daily patterns of feeding, with complete lesion of this area resulting in a significant loss of the circadian pattern of eating, with a nonsignificant decrease in the total amount of calories consumed [35].

Circadian Rhythms in Peripheral Tissues

While the SCN is viewed as the primary circadian pacemaker that regulates physiology and behavior throughout the rest of the body, recent discoveries have demonstrated that similar timekeeping mechanisms also exist throughout the rest of the body. We have previously discussed the rhythmic pattern of melatonin release from the pineal gland. In other species, such as birds, the pineal gland appears to play a key role in generating the free-running circadian rhythm, though that role appears to be less important in humans [36]. Interestingly, using a luciferase reporter gene, it has been demonstrated that multiple tissues throughout the body do exhibit rhythmicity in culture; however without the presence of the SCN, these rhythmic tissues are no longer synchronized with one another [37]. These daily rhythms are also

present in immune cells and cytokines [38], and glucocorticoids appear to be a primary synchronizing signal for these peripheral oscillators [39]. In addition, another major factor that can synchronize the timing of these peripheral clocks is the daily cycle of feeding-fasting. Feeding animals only at the "wrong time" of the day (i.e., during the habitual rest period) results in an inversion and uncoupling of the peripheral liver clock from the central SCN clock [40]. Furthermore, this uncoupling of the peripheral and central clocks appears to have negative physiological consequences [41]. As will be discussed further in the following section, these rhythmic peripheral clocks themselves can feed back to and influence the central SCN pacemaker.

There is also a circadian rhythm to the daily immune/inflammatory response, likely mediated by multiple factors, including the daily pattern of melatonin release and the circadian production of cortisol [42]. As was noted above, the pro-inflammatory cytokine TGF-α tends to be higher during the rest period, along with interleukin-1β, interferon-γ, and interleukin-6 [43]. Conversely, the anti-inflammatory cytokines IL-4 and IL-10 are higher during wake [44]. It is thought that this daily rhythm promotes a state of immunological memory formation during rest and a more localized immune response during wake (when focal injuries related to activity are more likely) [45] but may also be responsible for the increase in asthma attacks in the early morning and the worsening of atopic dermatitis symptoms at night.

Inputs to the Circadian Clock

Just as important as the ability to maintain an endogenous timekeeping mechanism is the ability to respond and adapt to changes in the environment. Multiple factors can provide input to the SCN in order to reset or entrain the primary circadian pacemaker with the surrounding environment.

The daily rise and setting of the sun shapes our daily schedule, so it is not surprising that the strongest factor that influences the circadian system is light. Most organisms have an intrinsic circadian period that is slightly longer or shorter than 24 hours, so the daily exposure to the environmental light-dark schedule serves to maintain appropriate alignment of physiology and behavior with the surrounding environment. Interestingly, mice bred to lack both rods and cones, the primary known photoreceptors in the retina, still exhibit a circadian response to light, suggesting the presence of additional photoreceptors [46]. This later led to the discovery in mammals that this light signal appears to be mediated primarily through a distinct set of photoreceptors in the retina, called intrinsically photosensitive retinal ganglion cells (ipRGCs), which contain a photopigment called melanopsin [47]. Melanopsin is most sensitive to light in the blue spectrum, around a wavelength of 480 nm [48]. When an animal is exposed to light, the signal is transmitted from the melanopsin containing ipRGCs, through the retinohypothalamic tract (RHT), to the ventral core of the SCN [49]. Rodent studies have demonstrated that this signal is transmitted using the neurotransmitter glutamate [50] and is mediated by induction of *Per1* and

Per2 [51]. Of note, as with all inputs to the circadian system, the response to a given stimuli is dependent on the circadian time at which the signal is received. For either nocturnal or diurnal animals, exposure to light [52] (or the neurotransmitter glutamate) [53] during the early evening, a time when light would normally be absent, causes the clock to delay or move later. Conversely, exposure to light during the early morning causes the clock to advance or move earlier. Under normal conditions these daily adjustments serve to help maintain entrainment between the endogenous circadian clock and the light-dark schedule of the surrounding environment. However we can also take advantage of these resetting properties clinically, by providing patients with appropriately timed light to advance or delay their clock as needed, whether related to jet lag, shift work, or the presence of a primary circadian rhythm sleep-wake disorder.

Melatonin is a hormone that serves both as an output of and marker of endogenous circadian time, as well as an input to the circadian clock that can serve as an input signal to adjust circadian timing. As was discussed earlier, melatonin production is regulated by the SCN, through hypothalamic projections to the intermediolateral column of the spinal cord, that then project through the sympathetic ganglia, back to the pineal gland. Melatonin levels are typically low during the day and rise shortly before sleep onset, a time referred to as the dim light melatonin onset (DLMO). In humans, low doses of melatonin (0.5 mg) ingested several hours before DLMO can advance or move the clock earlier. Conversely, melatonin ingested shortly prior to habitual wake time can delay or move the clock later [54]. In rodents placed in constant conditions [55], or in blind humans who lack photic input from light [56], timed melatonin administration can serve as an entraining mechanism to maintain a 24-hour schedule.

In addition to the two primary signals of light and melatonin, several other "non-photic" inputs to the SCN also exist. Many of these are better characterized in rodents than in humans. The first is activity. In rodents, activity occurring during times when they would normally be inactive can produce large phase shifts, typically shifting the clock several hours earlier [57]. These phase shifts appear to be produced in response to release of the neurotransmitter serotonin from the raphe nuclei [58, 59], possibly modulated by neuropeptide Y release from the intergeniculate leaflet (IGL) through the geniculo-hypothalamic tract (GHT) [60]. Exercise can also entrain peripheral clocks in the skeletal muscle and lungs [61]. The data is somewhat more complicated in humans and other diurnal organisms however. In *Arvicanthis* (a diurnal animal), serotonin increases rather than attenuates response to light [62]. Several studies in humans have demonstrated that evening exercise (after DLMO) can induce phase delays, while less consistent exercise prior to DLMO causes phase advances [63, 64]. Overall these phase shifts are of a much smaller magnitude than observed in hamsters.

Another non-photic factor that may contribute to entrainment is the daily pattern of feeding and fasting. The SCN regulates the pattern of feeding behavior and also regulates the processes involved in metabolism. The insulin-dependent response to glucose exhibits a circadian pattern, along with cycles of metabolism and catabolism within the liver [65]. However the peripheral clocks can also be strongly regulated by

the timing of feeding. Leptin is a hormone that inhibits hunger and exhibits a circadian pattern that can also be influenced by the daily patterns of caloric intake and sleep [66]. Leptin levels are decreased under conditions of circadian misalignment [67]. Studies have shown that leptin is also able to modulate the circadian response to light in female mice [68]. Interestingly feeding animals a high fat diet can increase the amount of time it takes to entrain to a change in light dark cycle, while a restricted calorie diet can increase the speed of entrainment [69]. Feeding rodents the same amount of calories but at the wrong time of the day (during their inactive period) can actually result in uncoupling of the peripheral oscillators from the central clock, so that they exhibit rhythms that are out of phase with the central clock, along with an alteration in the 24-hour core body temperature profile [40]. This may help to explain the increased risk for cardiometabolic disease observed among shift workers.

Summary

In summary, the circadian system represents a complex, tightly coordinated structure, present in nearly all organisms. In mammals the circadian system is regulated by the suprachiasmatic nucleus, which coordinates the activity of peripheral clocks throughout the body. Central and peripheral circadian timing plays an important role in multiple physiological processes, including regulation of the immune response, which could explain the variability of severity of allergic symptoms across the day and night. The circadian clock is uniquely responsive to various timekeeping stimuli at different times of the day, including exposure to light, melatonin, feeding, and activity. This system provides opportunities for future clock-based interventions for allergic disease.

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Overview and Understanding of Human Circadian Immunology

4

Nurcicek Padem and Anna Fishbein

Background

The circadian underpinnings of the immune system were first described in 1960 by Halberg and colleagues who demonstrated susceptibility to lethal infection in mice depending on time of day of infection [1], a finding partially mediated by endogenous corticosteroid levels [2]. Although animal studies make up the bulk of the circadian immunology literature, understanding immune rhythms via animal models is complicated by large differences from the human. For example, peripheral blood leukocyte counts peak during the day in mice and at night in humans (Fig. 4.1). Although the field of *human circadian immunology* is still in its infancy, this chapter will highlight key studies and hypotheses.

Human observations of the diurnal pattern of allergy and inflammatory disease make it clear that circadian immunology is central to many allergic (atopic) diseases. Specifically, most allergic diseases tend to flare overnight, as will be described in more detail throughout the book. The adaptive rationale for circadian rhythms of the immune system is that "immunity is a high-cost, high-benefit trait," in which the circadian clock serves as an important regulator to maximize benefit at time of day in which it is needed but minimize expending energy on immune reactivity when it is not generally needed [3].

Specifically, in Part I of this chapter, we address circadian rhythms of major cell types of the innate and adaptive immune system, including internal cell clocks, cell trafficking patterns, and influence of endogenous stimuli. In Part II, we expound upon the influence of exogenous stimuli (i.e., light, feeding time, etc.) on circadian

N. Padem
Division of Allergy & Immunology, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University, Chicago, IL, USA

A. Fishbein (✉)
Division of Allergy & Immunology, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: afishbein@luriechildrens.org

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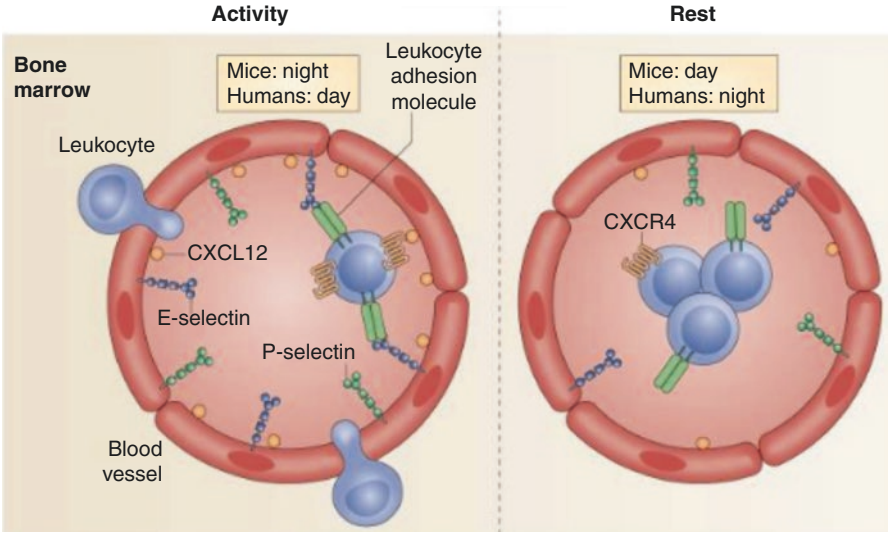


Fig. 4.1 Summary of leukocyte trafficking patterns in humans versus mice during sleep versus wake. Rest-activity cycles in diurnal humans and nocturnal mice. In murine bone marrow and skeletal muscle, leukocyte recruitment is enhanced during the active phase due to higher expression levels of chemokines as well as adhesion molecules on both the endothelium and hematopoietic cells. In peripheral tissues, the molecules oscillating on leukocytes mediating circadian recruitment are not known but likely include CCR2, the receptor for CCL2, and the ICAM-1-binding integrins LFA-1 and Mac-1. During the resting phase, lower adhesion molecule and chemokine expression as well as enhanced mobilization from the bone marrow result in reduced leukocyte recruitment and enhanced numbers of immune cells in blood (From Scheiermann et al. [49], with permission)

immunology. In Part III, we link circadian immunology to allergic disease. Although some key animal studies are described, this chapter focuses on basic and translational science in human circadian immunology. Clinical implications are summarized and covered in more detail in disease-specific chapters.

Part I: Internal Circadian Clock of Immune Cells, Cell Trafficking, and Influence of Endogenous Stimuli on Circadian Rhythm and Function of Immune Cells

Circadian Clock

As discussed in more detail in Chap. 3, the "circadian clock" refers to the molecular control of diurnal and nocturnal changes at the cellular and system level. The "clock" is made up of both peripheral and central components [4]. The central clock is found in the suprachiasmatic nucleus (SCN) and primarily driven by light exposure to the retina. This results in production of key synchronizers, such as melatonin and cortisol. Peripheral circadian clocks exist in almost all peripheral tissues and nucleated cells, including immune cells. The key regulators of the internal immune clocks include a set of highly conserved genes across species, most notably CLOCK (circadian locomotor

output cycles kaput) and BMAL1 (brain and muscle ARNT-like 1; also known as ARNTL) heterodimers [5]. These transcription factors induce the expression of Period (PER) proteins, crypotochromes (CRY), and REV-ERB nuclear receptors. These proteins then inhibit their own transcription via CLOCK-BMAL1 inhibition.

In human studies the expression of clock genes in immune cells and other peripheral tissues offers a method of studying peripheral circadian rhythms. Furthermore, the relationship with the immune clocks and markers of the central clock, such as melatonin, cortisol, and core body temperature, has helped to elucidate the relationship between "central and peripheral clocks" [6]. We will now describe the current state of the science of internal clocks and circadian homing mechanisms by cell type.

Monocytes/Macrophages

Macrophages are a key component of the innate immune system and act via various pattern recognition receptors, such as Toll-like receptors. TLR4, for example, recognizes LPS (lipopolysaccharides) and signals to induce an inflammatory response. In a mouse model, there are time-of-day-dependent changes in the macrophage [7] and TLR4 responses, which are controlled by clock gene Bmal1 [8]. These findings appear to be true in humans, in which the complex and tight regulation of innate immune responses by the circadian system leads to a variable response in pathogen challenges across the day [9]. Nguyen et al. demonstrated a critical role of the circadian clock, specifically Bmal1 in human Ly6C9(hi)monocytes for trafficking to sites of inflammation. They also noted that mice inoculated with *Listeria monocytogenes* had varying susceptibility to infection and death, depending on time of day they were infected. Indeed, the circadian-controlled monocyte trafficking predicted this susceptibility [10]. However their model did also note that the chemokine CCL2, which is induced when a pathogen is recognized, has a specific sensing mechanism to "turn-off" the normal circadian regulation of monocyte trafficking so that the host can switch to "defense" mode in anticipation of the pathogen.

Mast Cells

Mast cells are a key cell type in mediating allergic response. They are found in the mature form in specific tissues, such as the skin, gut, and other mucus membranes. The internal clock of mast cells has been demonstrated in cells purified from human intestinal tissue. These purified cells were noted to have rhythmic expression of core clock genes [11]. Several animal studies have advanced the functional knowledge of mast cell clocks in regulating allergic reaction, specifically in mouse models of passive cutaneous anaphylaxis [12]. Furthermore, mast cells have temporal gating of FCεR1 expression [13]. A recent study found that blocking the circadian pathway, via a selective casein kinase inhibitor, had similar effects to corticosteroid, i.e., there was suppression of IgE-mediated allergic reactions in mouse mast cells and decreased basophil reactivity in human basophils of allergic rhinitis patients [14]. This suggests an exciting role for circadian therapeutics in targeting allergic disease [15].

Basophils

Basophils are another key cell type in allergic disease primarily found circulating in peripheral blood. However, the basophil circadian story is not quite as clear as the mast cell story. Functionally, there is one study which suggests basophils have internal circadian clocks in animals and humans [16]. In this paper, they found circadian rhythm of basophil reactivity, i.e., CD203c expression and clock gene expression, suggestive of the time-of-day-dependent symptoms of allergic rhinitis. Furthermore, in healthy control subjects, CD63 expression in activated basophils had diurnal variation with decreased basophil sensitivity at 4 am compared to 4 pm; this was when assessed by mean fluorescent intensity of CD63+ [17]. In contrast, there was not a circadian rhythm to the percent of CD63+ cells in response to anti-IgE. This same group followed up this conflicting finding in allergic rhinitis patients. This time they studied basophils in allergic rhinitis patients, and still did not find a time of day difference in basophil activation testing via CD63 [18]. Taken together, these findings suggest that *if* there is a circadian influence on basophil responsiveness, it might be predominantly via CD203c, not CD63. Alternatively, mast cells (in contrast to basophils) might be the primary driver for circadian rhythms of allergic reactions, or there is a complex combination of factors of cells in local tissues in conjunction with the mast cells. However, the fact that selective inhibition of casein kinase (a key controller of circadian pathways) in human basophils decreased severity of allergic reaction suggests there is a circadian mechanism at play intrinsic to basophils. The relative contribution of the basophil and mast cell in relation to time of day differences noted in allergic disease certainly requires further study.

Neutrophils

Neutrophils are a component of the innate immune system which fight infection, resulting in oxidative burst and pus formation. Although not considered to be a classic "allergic" cell type, neutrophils are known as a biomarker for certain endotypes of asthma [19]. The necessity of circadian signaling in neutrophil chemotaxis has been demonstrated in animal models. Basically, the mechanism relies on endogenous glucocorticoids which bind to glucocorticoid receptors, inhibiting Cxcl5 transcription and reducing neutrophil infiltration. If clock gene Bmal1 is ablated in bronchiolar cells, there is exaggerated inflammatory response to LPS and *Streptococcus pneumoniae* [20].

Eosinophils

Eosinophils can be measured in peripheral blood but are found in much higher concentration in body tissues. Eosinophils are recruited by "allergic" innate lymphoid cells (ILC2) or T cells (TH2 cells) via IL-5, a pathway which is also used for fighting parasites. The time of day rhythm of eosinophils in peripheral

blood has been known for over 80 years, and more recently this circadian variation has been more strongly associated with IL-5 levels [21]. Local mechanisms involved in circadian gating include feeding timing which increases ILC2 expression of IL-5 and IL-13 and thus eosinophil recruitment in the gut via vasoactive intestinal peptide (VIP) or in the lungs. The internal circadian clock of human eosinophils is noted in molecular profiling from purified peripheral blood eosinophils [11]. These eosinophils were cultured, and clear oscillations in circadian clock genes were noted with in vitro cultures. This did not differ in atopic versus nonatopic subjects. Eosinophil-specific mediators, ECP and EPX, are also higher in night than the day [22], suggesting functional implication to eosinophil rhythms, i.e., increased nocturnal symptoms of allergic rhinitis and asthma. However, some studies have failed to demonstrate ECP and EPX are consistent biomarkers [23]. Overall, eosinophils appear to have rhythm in allergic and non-allergic patients; however, the functional consequences of these rhythms are not clear.

Natural Killer (NK) Cells

NK cells are not a key allergy cell type. They primarily fight viral pathogens, provide some cancer defense, and contribute to autoimmune disease. This cell type has a long circadian history, which is noted in the rhythm of autoimmune diseases (such as rheumatoid arthritis [24] and vitiligo [25]). NK cell activity peaks in the AM or afternoon and might contribute to the morning flare of rheumatoid arthritis [26, 27].

Innate Lymphoid Cells (ILCs)

Innate lymphoid cells protect again infection, support lymphoid formation, aid in tissue remodeling after damage, and can be a key contributor to allergic disease (type 2 innate lymphoid cells, ILC2). Very little data exists on circadian rhythms in these cells, but in mouse models, ILC2 are under circadian control in their ability to modulate time of day changes in eosinophils [21]. ILC3 cell homing is likely under circadian control via the transcription factor RUNX1 [28]. There is a known rhythm of aryl hydrocarbon receptors (AHR) and a time of day change in responsiveness [29]. It is speculated that this rhythm via AHR could serve as a target for regulating rhythm of ILCs.

Complement

Other components of the innate immune system, such as complement proteins, are under circadian control, with one study noting decreased C3 and C4 overnight as compared to the day, regardless of sleep [30].

Adaptive Immunity

Although we will discuss the intrinsic circadian clock of B and T cells, from animal studies, it is not clear if the intrinsic circadian clocks are necessary for appropriate trafficking, as B and T cells mostly respond to extrinsic circadian cues [31]. This is reflected in rhythms of other nonnucleated components in peripheral blood, such as red blood cells and platelets [32].

T cells

T cells (which mature in the thymus "T") are key lymphocytes that drive adaptive/cellular immunity. With regard to allergic disease, T cells play a key role in stimulating allergic inflammation, particularly CD4+ (T-helper cell) or CD8+ (cytotoxic T cell) TH2-type cells. The specific "allergic" subtypes (TH2) of CD4+ or CD8+ T cells are defined by the cytokine profile of these cells, classically IL-4, IL-5, IL-9, or IL-13 producing. Other T-cell types important in allergic disease, such as TH22 and TH9, are beyond the scope of this chapter.

T-cell Numbers

A few pivotal studies have characterized the T-cell circadian rhythm as measured in human peripheral blood [33–37]. Classically, cortisol nadir is described around midnight with peak lymphocyte counts around 2 am [38]. This timing appears to be true for naïve, effector memory and central memory subtypes [36]. The relative percentage of lymphocytes that are peripheral effector CD8+ T cells (CD45RA+CD62L− CD8+) peaks during the daytime (2 pm), correlating with epinephrine rhythms, a finding that can be induced by epinephrine infusion [36]. However, absolute peripheral effector T cells in one study had a nocturnal peak [27].

T-cell Function and Control

Furthermore, it is noted that in addition to rhythms of cell number, there is a rhythm to T-cell function. There is increased reactivity to adenovirus or *Staphylococcus aureus* B (SEB) during nighttime exposure [33]. However this relationship was not directly correlated to T-cell numbers, i.e., peak responsiveness to SEB occurred at night but earlier than peak in peripheral T-cell counts. Natural T-regulatory cells have also been shown to have a circadian rhythm, with a nadir in suppressive activity around 7 am, which is also a different rhythm than the overall counts [37].

In one human study, CD4+ T cells were isolated every 3 hours and stimulated non-specifically; a rhythm was noted to several cytokines. Specifically, the nadir (trough) of the CD4 cells' expression of interferon gamma (IFN-gamma), IL-4, IL-2, and even CD40 ligand (CD40L), occurred at 6 am [39]. A recent meta-analysis suggests that IL-6 cytokine, also, demonstrates variability in time of day measures. They found a trough in the AM [40].

Animal studies have also shown the development of T-cell subset TH17 is tightly regulated by the circadian clock. TH17 regulation occurs primarily via transcription factor NFIL3 which suppresses TH17 development and links to the clock via transcription factor Rev-erbα [41].

Mechanism, Including Effects of Endogenous Stimuli

T-cell number The mechanism driving the diurnal oscillations in T-cell distribution in peripheral blood versus lymph nodes, bone marrow, etc. is in part driven by glucocorticoid-induced upregulation of CXCR4 on T cells (Fig. 4.2). Expression of CXCR4 in the mouse lymphocyte is regulated by IL-7R expression in T cells [42].

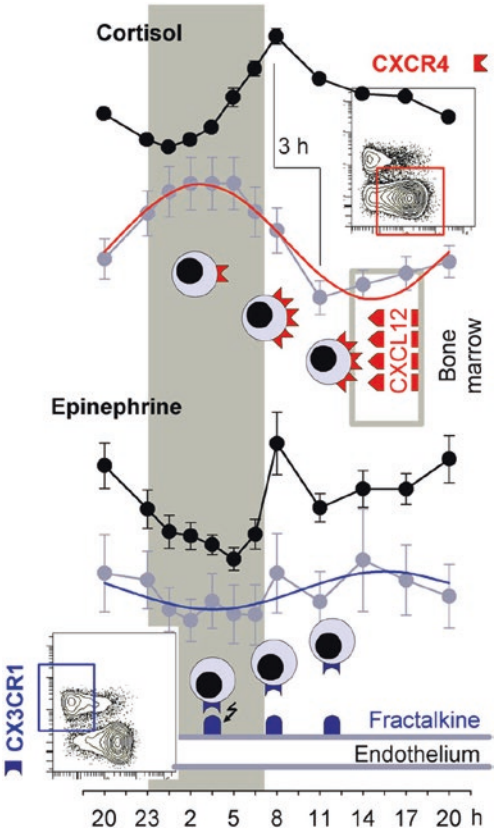


Fig. 4.2 Relationship between cortisol, epinephrine, and lymphocyte trafficking. Numbers of circulating T-cell subpopulations show opposing rhythms with a nighttime peak (represented by naive $CD4^+$ T cells; red cosine curve) or daytime peak (effector $CD8^+$ T cells; blue cosine curve). Circadian rhythms peaking at night are controlled through the release of cortisol, which strongly increases during the early hours of daytime and via GR activation (with a delay of 3 hours) redistributes T cells from the circulation to bone marrow. Rhythms peaking during daytime are controlled by release of catecholamines, which is increased during daytime, and via β-AR activation lead to an immediate demargination of the cells from the vascular endothelium. Cortisol-sensitive T cells are characterized by high CXCR4 expression, whereas epinephrine-sensitive cells show highest CX3CR1 expression. The two chemokine receptors mark two distinct T-cell populations with only few double-positive cells (contour plots for CXCR4 and CX3CR1 expression on $CD4^+$ [top] and $CD8^+$ T cells [bottom]). CXCR4 mediates homing of T cells to bone marrow with cortisol supporting this traffic by upregulating CXCR4. Available data on CX3CR1 tempt to speculate that this molecule facilitates margination of T cells to vascular endothelium, with epinephrine inducing demargination by suppressing adhesive fractalkine signaling (From Dimitrov et al. [36], with permission)

CXCR4 then binds to CXCL12 driving lymphocytes from the peripheral blood back to the bone marrow within a few hours [35, 42]. In the mouse model of lymphocyte trafficking via the lymph node, CCR7 enhances recruitment to the lymph node, and later S1pr1 drives lymphocytes out [35]. Additionally, the autonomic nervous system, primarily adrenergic (sympathetic) nervous system via epinephrine [36] and B2-adrenergic receptors [43], can mobilize effector CD8+ T cells into peripheral blood [36]. Animal studies suggest that it is the autonomic system that drives inflammatory changes in response to jet lag, leading to alterations in lymphocyte trafficking [44]. A recent human study simulated night shift in nine heathy adults by delaying bedtime by 10 hours and noted that 3 days of shift work did not significantly change cortisol, melatonin, or lymphocyte rhythms [45]. Although there was still a rhythm to cytokine secretion (besides IL-2), it was shifted (phase advanced) by about 5 hours in IL-1в, IL-6, TNF-α, and IFN-γ. Night shift increased levels of IL-2, but not of other cytokines.

T-cell function Although the mechanisms underlying circadian rhythm to T-cell function are not well explored, it appears in part to be mediated by intrinsic rhythm to the cell, i.e., the cell's clock (Table 4.1). Human studies clearly demonstrate a rhythm to circadian clock genes in peripheral blood mononuclear cells [46]. Furthermore, in determining the mechanism of cytokine rhythms from human CD4+ T cells, they found that rhythms of cytokine expression from CD4+ cells continued to be present ex vivo. The animal correlate study found that intrinsic cell circadian rhythm, potentially via nuclear factor kappa B (NF-KB) pathway, controls the cytokine expression time of day differences [39]. In allergic disease, cytokine expression might also be stimulated by endogenous melatonin levels (in addition to other exogenous stimuli, described later in this chapter). The authors suggest this is due to "higher responsiveness" of T cells and monocytes.

Table 4.1 Rhythms in immune cell function

Source	Oscillating parameter	Acrophase	Trough
Acrophase during the resting phase			
Blood	Neutrophils	CT20	CT8
Blood	Naïve, central memory and effector memory CD4+ and CD8+ T cells	CT2	CT14
Blood	HSCs	CT20	CT8
Blood	HSC mobilization from the bone marrow	Afternoon	Morning
Acrophase during the active phase			
Blood	Effector CD8+ T cells	CT14	CT2
Blood	Cortisol, adrenaline, noradrenaline	CT8–CT11	CT1–CT5
Naïve and central memory CD4+ and CD8+ T cells	CXCR4	CT9	CT21
Mature CD8+ T cells	CX3CR1	CT9	CT21

CT actual circadian time in hours (e.g. CT6 = 6AM), *HSC* hematopoietic stem cell, *CX3CR1* CX3C-chemokine receptor 1, *CXCR4* CXC-chemokine receptor 4
Adapted from Scheiermann et al. [49], with permission

B cells Although less well studied than in T cells, B-cell numbers in peripheral blood demonstrate clear circadian rhythms. Human studies demonstrate B-cell trafficking patterns which are predictable depending on the time of day. Several studies suggest, similar to T cells, there is a B-cell peak (or acrophase) at ~2 am in healthy adults [33, 38]. In humans, immunoglobulin class switch recombination to IgE ("allergic" antibody) is associated with a complex gene pathway involving over 1000 genes that are overall regulated by transcriptional factor BHLEHE40 (DEC1) [47]. DEC1 is a master regulator of germinal center activity and modulates circadian phase of gene expression [48, 49].

Part II: Effect of Exogenous Stimuli on Human Immune Function

Melatonin

Although many cite cortisol and epinephrine as the main drivers of leukocyte rhythms, melatonin is also an essential component of circadian immune regulation. As described in a review by Calvo et al. [50], melatonin (the main hormone which regulates circadian rhythms and is produced by the pineal gland) facilitates the complex bidirectional relationship between the immune system and the pineal gland. In fact, melatonin receptors are present directly on immune cells and on immune organs. An inflammatory stimulus resulting in internal upregulation of nuclear factor kappa B (NF-KB) will result in decreased melatonin synthesis in pinealocytes but increased in macrophages. As demonstrated in pinealectomy in animals (lack of melatonin expression but normal cortisol rhythm), there was an absence of circadian rhythm in leukocyte trafficking, with impaired delayed-type hypersensitivity (allergic) responses [51].

Many consider melatonin an antioxidant that is "anti-inflammatory". However, as it relates to allergic disease, exogenous melatonin is generally thought of as being "pro-inflammatory." Specifically in asthma, there are several studies which assert a pro-inflammatory effect [52, 53]. We hypothesize that the mechanism underlying the "pro-inflammatory effect" of either endogenous or exogenous melatonin in allergic inflammation is via melatonin which directly stimulates cytokine release from T cells [52, 54, 55]. This specifically occurs via melatonin binding to nuclear receptors of lymphocytes to decrease cAMP and enhance release of T-cell contents [50, 55–57]. In the case of "allergic cells," the cytokines released are TH2-skewed.

Despite the pro-inflammatory effects, there is growing interest in the potential sedative effect of melatonin, which could still be of benefit in some allergic patients to improve sleep [58, 59]. The relationship between melatonin and immunity in allergic disease certainly requires further study.

Feeding Timing and Food

Mixed results in animal studies make the relationship between feeding and immune function unclear. The postulated link between immunity and feeding is that feeding

entrains the circadian clock (i.e., is another cue to tell our body it is day and night), altering this timing. Specifically in mice, a study on monocyte rhythms demonstrated feeding cues do not entrain these rhythms [10]. In contrast to this, time-restricted feeding in a mouse model influenced innate immune responses, specifically with endotoxin exposure [60]. Interestingly a high-fat diet in mice might potentiate activation of pro-inflammatory macrophages [61]. Exacerbation of obesity in mice with BMAL1 deletion in adipose and liver tissue exemplifies the relationship between circadian clock and fat metabolism [62]. In one human study, variants of circadian rhythm-related genes such as melatonin receptor influenced fat distribution in the body [63]. Interestingly, feeding timing in mouse models alters the skin circadian clock [64]. Although unrelated to immune function, there is large body of literature on timing of food consumption, suggesting food consumption after 8 pm might increase the risk of obesity [65]. Taken together, these findings indicate timing of food intake and types of food consumed influence the immune system, and further research on this topic is needed to elucidate these complex relationships.

Exercise

Although exercise does not exert profound effects on the immune system, exercise will immediately increase lymphocyte subsets in the periphery, which will then go back to baseline levels within 40 minutes [66]. One small study suggests that plasma IL-6 and free fatty acids are higher in PM versus AM exercise groups, perhaps reflective of a higher metabolic benefit of PM versus AM exercise. However, other studies have found no time of day differences [67, 68]. Other circadian effects related to exercise include cardiovascular differences (i.e., blood pressure and heart variability) depending on time of day as a response to time of day differences in vagal response [69].

Light

With regard to the impact of light on the human immune system, to our knowledge, there are no large studies on this topic. From animal studies, we hypothesize that light has a profound effect on the immune system and in fact can reverse cortisol and resultant leukocyte rhythms. In fact, “day” lymphocytes transferred to a “night” animal and vice versa resulted in altered trafficking patterns of lymphocytes. Taken further, completely reversing an animal’s light and dark cycles (“jet lag”) completed reverses their lymphocyte trafficking patterns [35]. With regard to immune function, studies suggest that light exposure at night alters immunological responses such as bactericidal activity and might alter the response to antigen in models of delayed-type hypersensitivity [70, 71]. Further work in humans is needed to determine how we might use light as a therapeutic tool to improve immune function and the mechanisms by which light might be acting to induce changes in immune rhythms.

Sleep Deprivation (Further Detail in Chap. 1)

Most people will tell you they tend to get sick when they don't sleep enough. This finding has been demonstrated in several studies. Short sleep duration is associated with increased risk of the common cold; [72] furthermore adolescents with shorter sleep times are at higher risk for infection [73]. Acute sleep deprivation in college students decreased responsiveness to influenza vaccination [74]. Good sleep increases immunity to hepatitis A vaccination [75], and short sleep decreases likelihood of adequate immunity to hepatitis B vaccination [76]. Although the precise mechanisms behind these observations are not totally clear, one study found sleep regulates the suppressive activity of natural T-regulatory cells ($CD4+CD25^{high}$ lymphocytes) and sleep deprivation decreases this ability [37]. However, this article notes that FoxP3 expression was not time or sleep dependent.

Shift Work (Further Detail in Chap. 1)

The huge body of literature on shift work and its increased risk in metabolic disease, cancer, and infection has been the subject of several reviews [77–82]. Increased susceptibility to infection is likely secondary to both sleep deprivation and circadian misalignment in shift workers. To highlight studies on shift workers and immunity, one simple cross-sectional study noted an association between numbers of days of shift work and increased inflammation, i.e., increased counts of white blood cells, neutrophils, lymphocytes, and monocytes [83]. Timing of most cytokine peaks is significantly shifted in simulated shift work [45] and likely under less ideal alignment with actual pathogen exposure. In fact, simulated shift work induces circadian misalignment of key immune pathways such as natural killer (NK) cell responses [84]. The suppression of NK cell responsiveness probably also increases the risk of infection. Taken together, these papers suggest shift work leads to circadian misalignment, which results in mistimed responses to pathogens and immunity that is overall not functioning at maximal efficacy. Thereby, an increased risk of infection is potentiated in these often sleep-deprived shift workers. Although outside the scope of this chapter, shift workers are at risk for other inflammatory diseases, such as TH17-mediated inflammatory diseases (inflammatory bowel disease and psoriasis) [85–87].

Part III: Potential Clinical Implications in Allergic Disease

It is common to see worsening of allergic diseases overnight [88]. Classically, asthma symptoms are described to peak around 4 am (timing with lung function nadir and increased lymphocyte counts in the lung). Allergic rhinitis symptoms peak between 4 and 6 am when pollen counts are high, when in the recumbent sleeping position, and when other circadian factors are present (i.e., inflammatory rhythms), all of which result in increased edema of the upper airway. Atopic

dermatitis symptoms also appear to peak overnight, with peak scratching approximately 3 hours after bedtime [89].

Time can be harnessed to personalize therapy for allergic diseases, via *chronotherapy*. The practice of *chronotherapy*, or timed therapy, uses therapy in a more precise way. Understanding the circadian rhythms of the immune system will allow for more directed treatment of allergic disease. For example, in asthma timing of PM, leukotriene receptor antagonist therapy improves efficacy of the treatment (further details described in the chapter on chronotherapy). Even the risk of side effects from therapies can be adjusted by paying attention to time. Bavishi et al. described increased rate of cutaneous reaction rate to allergy shots (subcutaneous allergen immunotherapy) in the afternoon compared to morning [90].

In summary, immune cells have their own "circadian clock" and are under circadian control due to endogenous and exogenous factors, resulting in time of day differences in cell counts and function. Functionally human circadian immunology plays a crucial role in appropriate timing of vaccination, immunotherapy, treatment of infections, and exacerbation of inflammatory disease. Despite the breakthroughs described in this chapter, more work is needed. Specific areas would improve the care of allergic disease, including better knowledge of human immune rhythms and disease-specific research. Dr. Fishbein and her team have developed innovative approaches to the measurement of human immune rhythms. A personalized, timed-based treatment approach is in the future for allergic disease.

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Overview and Understanding of Allergic Reactions and Allergic Disease

5

Andrew M. Abreo, Kourtney G. Gardner, and Jonathan A. Hemler

Allergic disease refers to a broad collection of disorders that span multiple organ systems and differentially affect patients based on age. The typical progression of these diseases is called the "atopic march," starting with atopic dermatitis and food allergy at a young age and later development of asthma and allergic rhinitis (hay fever). Anaphylaxis and allergic skin diseases are also common. Allergic diseases represent an increasing burden to society. Approximately 25% of the population in industrialized countries suffers from one of these disorders, and the prevalence continues to rise [1]. Allergic rhinitis alone affects 13% of children and 14% of adults in the United States with an estimated direct and indirect cost of $7–8 billion annually [2]. These diseases are typically assessed via accurate clinical history and patient report, combined with specific IgE testing using skin prick to allergenic extracts or enzyme immunoassays on blood samples. In addition, asthma is assessed with objective measurements of lung function, such as spirometry [3]. Allergic diseases can also affect sleep, with allergic rhinitis being the most common allergic disease that contributes to decreased sleep quality due to nasal airway obstruction [4].

There are several theories as to why the prevalence of these diseases has increased, including the hygiene hypothesis. Originally proposed in 1989, this hypothesis suggests that decreased exposure to microbes leads to the development of allergic disease [5]. Although this theory has never been validated, it warrants discussion of the known mechanisms of allergic disease so we can better understand and treat these burdensome illnesses.

A. M. Abreo · K. G. Gardner
Division of Allergy, Pulmonary, and Critical Care, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

J. A. Hemler (✉)
Division of Allergy, Immunology, and Pulmonary Medicine, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN, USA
e-mail: jonathan.a.hemler@vanderbilt.edu

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Hypersensitivity Reactions

The major function of the immune system is to protect individuals from microbes and foreign substances. However, excessive immune responses against these antigens can lead to tissue injury. These responses, known as hypersensitivity reactions, manifest with variable severity. In 1963, Gell and Coombs grouped these reactions into four types based on the causative pathophysiology [6]. Type 1 reactions are mediated by immunoglobulin E (IgE) bound to mast cells and basophils. Antigen engagement of these antibodies induces the release and production of soluble molecules such as histamine and leukotrienes. This reaction is responsible for most allergic diseases, including systemic anaphylaxis, bronchial asthma, and allergic rhinitis. Type 2 reactions develop when antibodies target cellular receptors, cell surface antigens, or tissue-specific antigens. The effector mechanisms of this reaction include activation of the classical complement pathway, recruitment of leukocytes, and alteration of physiologic responses. Examples include autoimmune hemolytic anemia, Goodpasture syndrome, myasthenia gravis, and Graves' disease. Type 3 reactions occur when circulating antigen-antibody immune complexes are deposited throughout the body and induce inflammation. Examples include serum sickness, systemic lupus erythematous, and poststreptococcal glomerulonephritis. In contrast to other hypersensitivity reactions, tissue injury in Type 4 reactions is driven by T cell-mediated cytokine production and cytotoxicity. The tuberculin reaction and contact dermatitis induced by poison ivy or metals are examples of this reaction (See Table 5.1) [7].

Immunoglobulin E: Structure and Function

Immunoglobulin E (IgE) is a monomeric antibody involved in host defense against parasitic infections and the development of allergic diseases. IgE has a short half-life and is consequently the least abundant antibody isotype in circulation. Secreted and membrane-associated IgE molecules are composed of two light chains and two heavy chains, with each heavy chain expressing four constant regions (Cε1–4) [8]. Skin

Table 5.1 Types of hypersensitivity reactions

	Mediators	Target antigen	Effector mechanisms	Examples of diseases
Type I	IgE	Soluble antigen	Mast cell degranulation	Anaphylaxis, asthma, allergic rhinitis
Type II	IgG or IgM	Cell surface or tissue antigen	Complement activation, leukocyte recruitment, alteration of physiologic responses	Autoimmune hemolytic anemia, Goodpasture syndrome, myasthenia gravis
Type III	IgG or IgM	Soluble antigen	Immune complex formation and systemic inflammation	Serum sickness, systemic lupus erythematous, poststreptococcal glomerulonephritis
Type IV	T cells	Cell surface or soluble antigen	Cytokine production, cytotoxicity	Contact dermatitis, tuberculin reaction

prick testing is an effective and inexpensive method to detect the presence of specific IgE to allergens. Serum total and specific IgE levels can also be measured using various enzyme immunoassays. In these assays, immobilized allergens bind to specific IgE antibodies in a serum specimen. Enzyme-linked anti-IgE antibodies enable detection of allergen-specific IgE by measurement of signals from the labeled probes [3].

The development of IgE-mediated allergic reactions begins with the process of sensitization. Individuals are exposed to environmental allergens at epithelial barriers containing antigen-presenting cells. T follicular helper cells are activated upon antigen recognition in secondary lymphoid organs and proceed to activate antigen-specific B cells. Isotype switching and the production of allergen-specific IgE are mediated by the cytokines interleukin-4 (IL-4) and IL-13, both of which are produced in response to specific allergens. The heavy-chain constant region of the IgE molecule binds to the high-affinity FcεRI receptor on mast cells and basophils. Repeat exposure to the allergen leads to mast cell activation and the development of a damaging response characterized by an early and late phase [9]. This will be discussed later in the chapter.

Biochemical Mediators of Allergic Reactions

Allergic reactions involve cells of both the innate and adaptive immune systems, as well as a host of biochemical mediators that carry out their responses. Among these mediators are cytokines, which are secreted or membrane-bound, nonstructural proteins produced by a variety of cells. Cytokines enable communication between cells of the immune system and mediate inflammatory reactions. Important families of cytokines are summarized in Table 5.2. Chemokines are a particular type of cytokine which guide the movement of immune cells within the body.

Table 5.2 Major families of cytokines with representative examples and general functions

Family of cytokines	Major general functions	Examples of family members
Type I cytokines	Promotion of the growth, differentiation, and activation of T cells, B cells, and hematopoietic cells	IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-11, IL-12, IL-13, IL-15, IL-17, IL-21, IL-23, IL-25, IL-27, stem cell factor, colony-stimulating factors, and thymic stromal lymphopoietin
Type II cytokines	Antiviral defense, activation, or inhibition of other leukocytes, epithelial barrier function	Interferons, IL-10, IL-22
Tumor necrosis factor (TNF) superfamily cytokines	Inflammatory response, generation of lymphoid organs, and survival and proliferation of B cells	TNF, lymphotoxins, B cell-activating factor
IL-1 family cytokines	Inflammatory response, activation of various cells including leukocytes and endothelial cells	IL-1, IL-1 receptor antagonist, IL-18, IL-33
Other transforming growth factor-β (TGF-β)	Promotes tissue repair and the differentiation of regulatory T cells and Th17 cells; inhibits other T cell subsets, B cells, and the activation of macrophages	TGF-β

Helper T cells of the adaptive immune system include several subsets with distinct functions, all of which are derived from a common precursor. The development of an allergic response depends on the activation of a specific subset of helper T cells, known as Th2 cells, which produce the cytokines IL-4, IL-5, and IL-13 in response to antigens in the environment. These cytokines function to promote an inflammatory response within tissues. An innate immune cell, known as the eosinophil, is recruited to these tissue sites by IL-4 and activated by IL-5. In the late phase of an allergic response, mucus secretion is increased by IL-13-induced stimulation of epithelial cells [10]. Type 2 innate lymphoid cells, or ILC2s, also produce IL-5 and IL-13 and may play a similar role in the development of allergic disease. While there is a genetic predisposition for developing Th2-mediated responses to environmental antigens, the exact reason why some individuals mount these allergic responses and others do not is not fully understood.

Mast cells are bone marrow-derived cells of the innate immune system that contain cytoplasmic granules that are released when these cells are activated. While they serve a crucial role in anthelminthic immunity, activation of these cells is also important in allergic responses. As previously discussed, IgE plays a large role in allergic disease. IgE antibodies against allergens interact with mast cells via IgE receptors and become attached to the surface of these cells. When this mast cell-bound IgE encounters its allergen, these IgE receptors are cross-linked, causing release of mast cell cytoplasmic granules. These granules contain products, including histamine, platelet-activating factor, prostaglandin D2, leukotrienes, and a variety of cytokines, which play an integral role in the early phase allergic response. Histamine is a vasoactive amine, which acts on blood vessels to produce vasodilation and increased vascular permeability and vascular leak. Another function of histamine is the induction of smooth muscle contraction in the gastrointestinal and respiratory tracts, leading to increased peristalsis and bronchoconstriction, respectively. Platelet-activating factor (PAF) is a lipid mediator derived from membrane phospholipids, which is produced by mast cells, endothelial cells, platelets, and other cells of the innate immune system. As its name suggests, it has a role in platelet aggregation and can trigger thrombotic cascades, blood vessel dilation via smooth muscle relaxation, and a decrease in blood pressure. In allergic responses, PAF can also induce bronchoconstriction [10]. The cyclooxygenase pathway in mast cells produces prostaglandin D2 (PGD2), which induces bronchoconstriction, vasodilation, and recruits neutrophils to the site of inflammation. The lipoxygenase pathway in mast cells produces leukotrienes, which lead to smooth muscle contraction in the upper and lower airway; this produces bronchoconstriction and nasal congestion. Together, these mast cell mediators are responsible for the symptoms of anaphylaxis, which can include hives, swelling, wheezing, nasal congestion, abdominal cramping, vomiting, diarrhea, and hypotension in response to allergens such as insect stings or food ingestions in allergic individuals [7].

Eosinophils are another bone marrow-derived innate immune cell involved in allergic responses. Like mast cells, eosinophils also contain cytoplasmic granules that are released upon cellular activation by antigen. Eosinophils typically reside in peripheral tissues but can be brought to sites of inflammation via the collective work of adhesion

molecules and chemokines. The expression of adhesion molecules is enhanced by the cytokine IL-4. A chemokine known as eotaxin is produced by epithelial cells at sites of allergic reaction and draws eosinophils to these locations. As previously mentioned, IL-5 is made by Th2 and ILC2 cells, and activates eosinophils allowing greater release of their granule contents. The granules of eosinophils contain cationic proteins and enzymes. Major basic protein and eosinophil cationic protein are cationic granule proteins which are toxic to helminths and bacteria. Eosinophil peroxidase is an enzyme within these granules that catalyzes the formation of hypohalous acids, which are also toxic to parasites. In addition to being toxic to parasitic invaders, these substances can also damage nearby host tissues. Activated eosinophils may produce several other mediators which are also produced by mast cells, including PAF, prostaglandins, and leukotrienes. Together, these mediators contribute to the pathologic manifestation of allergic disease [11].

Types of Allergic Diseases

The severity of an allergic reaction varies based on the route and concentration of allergen exposure. Systemic anaphylaxis is the result of diffuse mast cell activation in response to an allergen. Progression to anaphylactic shock is characterized by hypotension, bronchoconstriction, or laryngeal angioedema. Epinephrine should be administered at the first sign of anaphylaxis. Inhalation of environmental allergens can induce mast cell activation in the epithelium of the respiratory tract. Symptoms range from sneezing and nasal congestion in allergic rhinitis to airflow obstruction and respiratory distress in allergic asthma. Food allergy results from the activation of mast cells within the gastrointestinal tract in response to ingested food allergens. Symptoms may be isolated to vomiting and diarrhea; however, systemic absorption can lead to anaphylaxis. Cutaneous exposure to allergens may induce urticaria, or hives, mainly due to the effect of histamine on the local tissue environment. Atopic dermatitis is associated with skin barrier defects that enable environmental allergens to promote a chronic inflammatory reaction [7, 10]. The impact of these allergic diseases on various aspects of sleep will be discussed in greater detail throughout the remainder of this book.

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Ontogeny of Sleep in Infants, Children, and Adolescents

6

Irina Trosman, Samuel J. Trosman, and Stephen H. Sheldon

Sleep is a cyclic, physiologic state characterized by decreased responsiveness associated with behavioral and physiological changes from which individuals arise spontaneously [1]. Behavioral changes during sleep include, but are not limited to, eye closure, postural changes, and a reduction in response to stimuli. Despite behavioral quiescence, brain activity during sleep is intense. In fact, the brain is considered to be more active during sleep than during wakefulness. Infants and young children spend a majority of their time asleep, suggesting that sleep is extremely important for the developing brain and body. Changes in sleep architecture and the overall amount of time spent asleep are most remarkable during early childhood. The pattern of change, or sleep ontogeny, correlates with critical periods of brain maturation [2].

I. Trosman (✉)
Sleep Medicine Center, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: itrosman@luriechildrens.org

S. J. Trosman
Department of Otolaryngology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

S. H. Sheldon
Departments of Pediatrics & Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Sleep Medicine Center, Division of Pulmonary and Sleep Medicine, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

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Infant Sleep

The earliest studies of sleep and wakefulness in infants were based on the observations of caregivers [3, 4]. Breakthrough research in infant EEG during the 1950s helped combine behavioral observations with EEG findings and lead to the discovery of REM sleep [5].

Later, in addition to EEG activity, researchers added the monitoring of extraocular movements (EOG), chin myogram (chin EMG), motor behavior, and respiration to sleep studies. Based on the data analysis, they were able to identify three primary behavioral states: (1) wakefulness, characterized by an activated EEG, high muscle tone, and gross body movements; (2) quiet sleep (QS), characterized by EEG delta waves (also known as slow waves), decreased muscle tone, and behavioral quiescence; and (3) active sleep (AS), characterized by an activated EEG, absence of muscle tone, rapid eye movements, and myoclonic twitches. Quiet sleep is also called NREM or NR sleep. Active sleep is interchangeably called REM or R sleep.

In addition, normal infants were found to have periods of sleep not easily categorized as a particular sleep state because of the overlap of features in the sleep and awake states present concurrently. These periods were variously called transitional, indeterminate, or intermediate sleep [6].

The normal, full-term newborn sleeps approximately16–18 h per day. The pattern of sleep and wakefulness is irregular, with a maximum continuous sleep period of 2.5–4.0 h that is often synchronized with feeding times [7]. The circadian rhythm is not fully developed. Sleep cycles consist of both active and quiet sleep periods in equal proportion. Each cycle lasts 50–60 min, and sleep onset occurs through active (REM) sleep [8]. Night wakings commonly experienced by infants typically occur at the end of each sleep cycle [9].

In the first few months of life, infants develop the ability to sustain longer periods of more consolidated sleep and waking [10, 11]. Most infants eventually begin sleeping longer hours at night. A consolidated sleep episode throughout the night is considered a major developmental milestone [9]. Although the average total sleep duration remains fairly constant across the first year of life (approximately 14 hrs per day), one of the most fascinating features of infant sleep is the large variability of sleep patterns among infants [12, 13].

Individual differences between infant sleep patterns had been observed by sleep researchers decades ago [14]. These differences were attributed to mother-infant interactions or to other factors such as the infant's positioning during recording [15, 16], the thermal environment [17], and phototherapy [18]. In addition, sensory stimulation was found to contribute to a possible variability in infant sleep patterns. Some researchers speculated that a continuous white noise helped induce sleep [19, 20].

Active Sleep/REM or (R) Sleep

Recognizable EEG patterns of REM and NREM sleep first appear at 32–34 week of conceptional age (CA), though the behavioral correlates of REM sleep are seen as

early as 28–30 w CA [21]. During REM sleep, the EEG pattern resembles a wakefulness pattern, chin muscle tone (EMG pattern) is reduced, and bursts of vertical and horizontal saccadic eye movements are noticed. Heart and respiratory rates are rapid and irregular. The lack of chin muscle tone, attributed to immaturity of skeletal muscle atonia development, is frequently used to distinguish REM sleep from wakefulness [21].

The distinction between wakefulness and REM sleep can be challenging due to similar EEG activity. Infant REM sleep behaviors include sucking; facial grimaces; clonic jaw jerks; fine limb muscle twitches; chin, body, and limb tremors; intermittent stretching; and irregular respiration. These behaviors are also observed in wakefulness. One of the most prominent REM sleep researchers, Dr. Howard Roffwarg, was surprised by striking similarities between infant REM sleep and wakefulness behaviors. He stated: "Through the ages, mothers have believed that after feeding, as the infant lies there in repose, gurgling and smiling, arching an eye, that he's expressing contentment with the feeding. In fact, it has nothing to do with nourishment; he's simply gone into rapid eye movement sleep and all the facial expressions are simply part of the phasic muscular discharge activated by the brain in REM sleep" [22].

NREM Sleep (N) or Quiet Sleep

In contrast to REM sleep, NREM sleep is characterized by more organized patterns of physiological inhibition. Both respiratory and heart rates are slowed and more regular. The EEG is synchronized with specific lower frequency waveforms. In infants, NREM sleep is also called quiet sleep.

Neonates in quiet sleep show an EEG pattern known as tracé alternant. Tracé alternant is defined by bursts of high-amplitude slow-wave activity interspersed with low-voltage activity [23]. While older infants also exhibit a quiet sleep state, the tracé alternant disappears by 46–48 weeks' postconceptional age [24].

Sleep and Infant Learning

REM sleep in utero is frequently associated with muscle twitches. Studies done in human infants and infant animal models revealed an association between limb twitching and the organization of spinal sensorimotor circuits and regions of the developing somatosensory cortex [25].

Newborns spend up to 70% of their time asleep [26]. When compared to adults and older infants, newborns spend much more time in REM sleep, accounting for almost half of their total sleep time. The REM sleep percentage in preterm infants is even higher, accounting for 70–80% of the total sleep time [27].

Why do infants spend so much time in sleep and in REM sleep in particular? After birth, the human infant is considered to be one of the least neurologically mature mammals [28]. An astonishing 75% of human brain growth occurs postnatally.

The first few months of life are a time of rapid learning about the environment. However, there are limited waking hours available for environmental exploration. This likely implies that a significant amount of learning occurs during a neonate's sleep [21].

Research suggests that sleep is extremely important for learning and memory. Brief periods of wakefulness are followed by periods of sleep, during which memory consolidation likely takes place. Interestingly, some research suggests that infants have the capacity to learn new information while asleep [29].

Some researchers argue that myoclonic twitches during REM sleep in infants represent a form of motor exploration which helps infants explore limb biomechanics, build motor synergies, and lay a foundation for complex, automatic, and goal-directed movements when awake [30].

REM sleep disruption and/or reduced time spent in REM sleep during early infancy has lasting effects on later cognitive functioning [31–33]. Less interrupted sleep and more time spent in REM sleep were associated with better cognitive outcomes. One prospective study of premature infants found that preemies who slept poorly as neonates exhibited poorer attention and greater distractibility at 4 and 18 months than those who slept well [33]. These findings have prompted interventions to improve infant sleep in neonatal intensive care units, including environmental noise reduction, lights dimming at night, and nonpharmacological treatments for pain [34–38].

Researchers studying sleep development speculate that the understanding of sleep ontogeny may provide insight into neonatal sleep pathologies, such as sudden infant death syndrome (SIDS) [39]. Some investigators hypothesized that infant learning from parent-infant contact throughout the night may help to prevent SIDS [40]. For instance, one study of mothers and their 2- to 4-month-old infants recorded and analyzed mother-infant sleep patterns simultaneously as they slept in the same bed in the sleep laboratory [28, 41]. The sleep patterns of mother-infant pairs were recorded again as each pair moved from two nights of solitary sleep in adjacent rooms to a third night during which they slept in the same bed. The findings revealed that co-sleeping mothers and infants experienced more arousals on average than they do when sleeping alone. In addition, an analysis of sleep patterns revealed more frequent stage shifts (moving from one stage of sleep or awake status to another). Co-sleeping infants spent less time in nonrapid eye movement (NREM) stage 3 compared to when they slept alone. Based on these findings, the authors suggested that co-sleep learning might provide the infant with increased opportunities to practice arousals. It was speculated that the ability to become more proficient at arousals might play a key role in SIDS prevention [40].

Full-Term Healthy Human Newborns Architecture Summary

- Full-term neonates sleep at least 16–18 h per day. Seventy to 80% of sleep time in preterm infants and 50% of sleep time in term infants is spent in REM sleep [25].
- The circadian rhythm is not fully developed, so sleep can occur as easily during the daytime hours as during the night. The pattern of sleep and wakefulness is

irregular with a maximum continuous sleep period of 2.5–4.0 h, often synchronized with feeding times.
- In newborns, only two sleep states – REM sleep and NREM sleep – can be distinguished. When sleeping infants do not show the sustained, specific pattern of physiological and behavioral activity characteristic of either quiet or active sleep, they are said to be in indeterminate sleep.
- It has been hypothesized that R sleep plays an important role in memory consolidation and learning. The high prevalence of active sleep during early infancy, a period of rapid brain development, seems consistent with this hypothesis.
- REM and NREM sleep states alternate during sleep cycles that recur periodically throughout the sleep period, cycling approximately every 50 min.
- Sleep begins with an initial REM period, and each sleep cycle includes an approximately equal amount of REM sleep and NREM sleep.

Older Infants and Young Children

By 6 months of age, an infant's sleep architecture more closely resembles that of an adult. Nighttime sleep gradually becomes consolidated over the first year into a single continuous block, and daytime sleep gradually decreases over the first 3 years. Sleep cycles gradually increase in length from 50–60 min in infancy to 90–110 min. By the age of 4 years, most children no longer require a daytime nap [9]. These changes in sleep patterns from the fetal period through late infancy have been attributed to the maturation of multiple neural networks [42].

NREM sleep also becomes more diverse. Specific EEG waveforms are used to subclassify the three stages of NREM. Non-REM sleep is divided as follows:

- *Stage 1 sleep*. This stage is often referred to as "light sleep" and frequently occurs at the sleep-wake transition. It typically lasts 30 s to 5 min and occupies about 5% of total sleep time. The EEG of stage 1 NREM sleep resembles the tracing of REM sleep; however, respiratory and heart rate patterns are regular and saccadic eye movements are absent. The lowest arousal threshold (easiest to awaken) is in stage 1 sleep [9].
- *Stage 2 sleep*. It is considered to be deeper sleep. The EEG of stage 2 NREM sleep contains *K complexes* and *sleep spindles*. It occupies about 45 to 55% of total sleep time (TST).
- *Stage 3 sleep*. It is known as "deep" sleep, slow-wave sleep (SWS), or delta sleep. EEG during SWS contains slow, high-voltage synchronized delta waves. Respiration is slowest and most regular during this stage. It is nearly impossible to wake children during SWS of the night's first sleep cycle. In one study, a 123-dB tone failed to produce any sign of arousal in a group of children whose mean age was 10 years [43].

SWS occupies about 25% of total sleep time and usually takes place during the first half of the night. Parasomnias (sleepwalking, confusional arousals, and night

terrors) usually arise from slow-wave sleep and are typically observed during the first few hours following sleep onset. Preschool age children are at higher risks of parasomnias due to the higher proportion of slow-wave sleep in this age group [9]. Children up to mid-adolescence often "skip" their first REM episode, likely due to the quantity and intensity of SWS activity early in the night [44].

The last half of the night is usually spent predominantly in stage 2 NREM and REM sleep [7].

Sleep-related events such as frequent awakenings from sleep, sleepwalking, and sleep terrors are common in childhood. Understanding sleep developmental changes helps the clinician distinguish normal age-appropriate changes from pathology, make accurate diagnosis, and provide appropriate guidance.

Changes Occurring in Late Childhood and Adolescence

Slow-wave sleep (SWS) percentage gradually decreases with age (Carskadon and Dement) [45]. The amount of SWS correlates with sexual maturity stage and decreases by approximately 35% between Tanner stage 1 and Tanner stage 5 [46].

Research suggests that the amount of SWS correlates with the development of neuronal synopses [47]. The highest number of synapses per neuron is 2500 at birth. An infant's brain contains approximately 100 billion neurons. New synapses are added after birth, and by age of 2 or 3 years, the number of synapses has grown to 15,000 per neuron. However, such synaptic density may place the brain at risk for synaptic overload and reduced synaptic efficiency. "Overload reduction," or pruning, is the process of elimination of extra neurons and synaptic connections in order to increase the efficiency of neuronal transmissions. Pruning occurs preferentially during sleep and is usually complete by age 11, with 40% of synapses in the brain eliminated [48]. The quantity and amplitude of SWS (NREM 3) across a night appear to follow brain neuron synapse development and pruning. SWS absolute values follow an inverted U curve, with a progressive increase between ages 6 and 8 years, a peak at 8 years, and a significant decline by more than 60% between ages 12 and 16.5 years [49–51]. This massive decline in SWS likely reflects the extensive elimination of unnecessary cortical synapses that occur during adolescence; however, more evidence is needed to confirm this [47].

It has been speculated that insufficient sleep during adolescence may lead to improper pruning [47]. Chronic sleep deprivation and subsequent improper pruning may result in aberrant wiring or inadequate consolidation of memory and learning, which some hypothesize may contribute to psychiatric disorders such as schizophrenia [52].

By mid-adolescence, children no longer skip their first REM sleep period, and sleep more closely resembles an adult sleep pattern [44].

A continuous decrease in total sleep time through middle and late adolescence of approximately 2 h has been described by some researchers [53], yet other studies show that adolescent total sleep time requirements do not really change with the maturation state. Delayed sleep onset and reduced total sleep time (due to social

reasons such as a delayed bed time and early morning wake up time) result in a cumulative sleep debt and cause reduction in adolescents' daytime alertness (as measured by multiple sleep latency test).[45, 54].

Total sleep time in older children is determined by genetic factors, race, socioeconomic factors, and cultural beliefs as well as coexisting medical conditions. For example, several studies have found racial differences in adolescents' sleep duration, with African-American adolescents achieving less sleep than other racial groups [55, 56]. These differences persist after controlling for SES, napping, and family functioning variables. A study of napping among healthy children found that white children nap significantly less frequently than African-American children and have longer bouts of nighttime sleep, though total sleep duration was nearly equivalent [57]. Asian adolescents' bedtimes were later than their peers from North America and Europe on school nights, resulting in less total sleep time and a higher level of daytime sleepiness. The duration of sleep on weekends was fairly consistent worldwide, with bedtime 2+ hours later and more total sleep time at night. The pattern of a delayed bedtime consistent with delayed sleep phase disorder was observed in adolescents across the world [58].

Sleep duration during early and middle childhood may vary considerably [59]. One UK study demonstrated a wide range of sleep duration, from 10–17 h in early infancy narrowing to 8.5–11 h in healthy 11-year-olds [60].

Chronic illness may also be an independent risk factor for sleep problems, affecting both sleep quality and sleep duration. For example, children with asthma are more prone to anxiety and depressive symptoms [61]. While this relationship is complex, the presence of nocturnal asthma symptoms may increase anxiety and affect sleep (McQuaid) [61].

General Statements Regarding Sleep in Older Children and Adolescents

- Continuous decrease in total sleep time.
- Sleep is entered through NREM sleep.
- NREM sleep and REM sleep alternate during periods lasting approximately 90 min.
- SWS predominates during the first third of the night and is linked to the initiation of sleep and the length of time awake.
- REM sleep predominates during the last third of the night and is linked to the circadian rhythm of body temperature.
- Wakefulness in sleep usually accounts for less than 5% of the night.
- Stage 1 sleep generally constitutes approximately 2–5% of sleep.
- Stage 2 sleep generally constitutes approximately 45–55% of sleep.
- Stage 3 sleep generally constitutes approximately 20–25% of sleep.
- NREM sleep, therefore, is usually 75–80% of sleep.
- REM sleep amount remains unchanged, usually 20–25% of sleep.
- REM periods occur in four to six discrete episodes, with the longest episode taking place at the end of the night.

- Adolescents may develop daytime sleepiness. This change correlates with sexual development and may be related to an insufficient amount of sleep time obtained at night.
- Considerable differences in sleep habits and patterns have been observed between children. Total sleep time in older children is related to genetic factors and impacted by socio-economic and cultural factors, as well as a child's medical problems.

Conclusions

Changes in sleep architecture and the overall amount of time spent asleep are most remarkable during early childhood. The pattern of change, or sleep ontogeny, correlates with critical periods of brain maturation. Research suggests that sleep is extremely important for learning and memory. Genetic, environmental, cultural, behavioral, and medical factors as well as individual variations in a child's sleep developmental pattern can all impact sleep physiology and pathology. There are still many unanswered questions regarding sleep development and the overall role of sleep. The understanding of sleep ontogenesis and function may help elucidate sleep's complex role in childhood development, diagnose sleep disorders, uncover their etiology, and prevent their long-term sequelae.

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Part II

Clinical Science

7 Screening for Allergic Disease in a Child with Sleep Disorder and Screening for Sleep Disturbance in Allergic Disease

Tanvi H. Mukundan

Allergy and Sleep

The three most common allergic conditions that impact sleep and that sleep in turn impacts are asthma, allergic rhinitis, and atopic dermatitis. These allergic diseases are triggered through a common pathway stemming from IgE that leads to a type 1 hypersensitivity reaction. This begins when susceptible individuals are exposed to a protein-based allergen. This allergen leads to an inflammatory cascade through an increase in production of T-helper type 2 cells which in turn produce several inflammatory cytokines including interleukins 4, 5, and 13 [1]. These inflammatory mediators not only lead to asthma, allergic rhinitis, and atopic dermatitis, but they can also have an impact on sleep as well as daytime function. The presence of these inflammatory mediators can cause aberrations in REM sleep including increased REM latency and decreased REM duration. Additionally, the inflammatory cascade triggered by allergic sensitization has also been demonstrated to cause increased arousals from sleep [2]. These findings have been found both in the sleep lab and in patient complaints. Children with allergic disease have been shown to have difficulty falling asleep resulting in prolonged sleep latency and difficulty staying asleep resulting in increased sleep fragmentation. During the day, these atopic (allergic) children then complain of excessive daytime sleepiness that can negatively impact their behavior [3]. Similar findings have borne out when examining populations of children who have experienced wheezing in the last year, those with chronic cough, and/or rhinitis compared to controls; they experience worse sleep quality, restless sleep, and daytime sleepiness [4, 5]. Similarly, children with excessive daytime sleepiness have a higher prevalence of atopic disease as, in a recent study, the fourth highest risk factor for excessive daytime sleepiness in children was asthma [6].

T. H. Mukundan (✉)
Department of Sleep Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

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In addition to fragmented sleep and daytime sleepiness, sleep-disordered breathing and allergic disease tend to be common comorbidities. Sleep causes relaxation of the pharyngeal dilator and constrictor muscles causing increased airway resistance; however, this alone does not lead to sleep-disordered breathing. Sleep-disordered breathing occurs when the collapsible portion of the airway experiences greater pressures outside of the airway than in the lumen of the airway [7]. This collapse can happen in a number of circumstances; however, in children with allergic disease, it often occurs due to nasal congestion. Nasal congestion leads to even further narrowing of the airway causing increased negative pressure on inhalation, nasal collapse, and finally airway obstruction [8]. Thus, children with allergic disease more often have a positive Pediatric Sleep Questionnaire, a screening tool used to evaluate for sleep-disordered breathing, than controls [9]. The impact of sleep-disordered breathing on sleep quality and daytime function can be profound, so sleep-disordered breathing should be evaluated for in children presenting with allergic complaints.

Asthma and Sleep

Asthma's impact on sleep has been extensively studied both in adults and children. Nocturnal asthma has an especially profound effect on sleep. Not only are nocturnal symptoms of asthma indicative of overall poor asthma control; they can also cause significant sleep fragmentation and increased time spent awake [10]. These children are also more likely to experience school truancy and worse school performance than children without nocturnal asthma symptoms [11]. However, nocturnal asthma is not the only type of asthma symptom that correlates with poor sleep quality. Multiple adult and pediatric studies have shown that those with asthma in general have increased sleep disruption, increased difficulty falling asleep, shorter sleep duration, and worse sleep quality than individuals without asthma [4, 12, 13]. An adult study showed that patients with asthma were twice as likely to have difficulty falling asleep and experience a greater frequency of undesirable early morning awakenings. Likely due to these sleep aberrations, these patients were one-and-a-half times more likely to experience excessive daytime sleepiness [14]. Other pediatric studies have demonstrated that children with asthma were over two times as likely to experience nocturnal enuresis and increased movements during sleep [15, 16]. These children also have more difficulties with daytime function as they tend to experience more daytime sleepiness and take more naps compared to non-asthmatic children [17, 18]. Their poor sleep quality seems to correlate with worse performance on memory and concentration tasks, increased fatigue, and ultimately more psychological and neurobehavioral issues [16, 19]. Even children without a formal diagnosis of asthma, merely those who have experienced an episode of wheezing in the last year, have more restless sleep than children who have not wheezed [4, 20]. Thus, it is crucial for these patient's medical providers to be aware of the impact that wheezing and asthma can have on nighttime sleep and daytime function. Additionally, when asthma is well controlled, many of these sleep difficulties can be partially ameliorated [21].

In addition to understanding how asthma can impact sleep quality and daytime function, it is imperative to appreciate the high prevalence of sleep-disordered breathing and sleep apnea in patients with asthma and the negative consequences that sleep apnea can have on asthma control. Asthma patients are at higher risk of sleep-disordered breathing, and similarly, sleep-disordered breathing is present in a large percentage of these patients [22]. Worse control of asthma correlates with worse sleep apnea severity. Conversely, patients with sleep apnea have more difficulty controlling their asthma [23–25]. In adult patients with difficult to control asthma, the prevalence for sleep apnea has been found to be as high as 75% [26]. In addition, one study found that asthma is prevalent in about 35% of adults with sleep apnea [27]. Pediatric studies show sleep-disordered breathing to be present in nearly 30% of all asthmatics with the rates increasing to 63% for patients with poorly controlled asthma [28, 29]. Additionally, asthma appears to make sleep apnea worse as children with asthma and sleep apnea have worse REM-related obstructive episodes than children with sleep apnea alone [30].

Sleep apnea also affects the morbidity of asthma. Asthma is one of the leading causes of hospitalization in children. Children with asthma complicated by obstructive sleep apnea are at much higher risk of prolonged inpatient hospitalization [31]. Patients with sleep apnea and asthma also have more frequent and more severe asthma exacerbations [32]. While the pathophysiology of this is not fully understood, treatment of sleep apnea seems to reduce asthma severity. Multiple studies have demonstrated that children who have their tonsils and adenoids removed to treat sleep apnea have a reduction in asthma symptoms, decreased rescue inhaler use, and fewer asthma exacerbations [28, 33].

Allergic Rhinitis and Sleep

Allergic rhinitis is a prevalent cause of sleep disturbance and can predispose an individual to sleep apnea. Many patients endorse worsening of their allergic rhinitis when sleeping. This may partially be due to allergen exposure in the home environment or from bedding material but also is contributed to by the typical recumbent position associated with sleep. This position can worsen nasal congestion due to an increase in nasal turbinate edema [34]. The impacts of this congestion are profound. Patients with allergic rhinitis report worse sleep quality, worse quality of life, and poor work performance, findings that have been borne out in multiple large-scale adult studies [34–36]. While fewer studies have been conducted in children, similar results have been found. In general, about 13% of children have allergic rhinitis. Up to 40% of these children have difficulty with sleep including difficulty falling asleep and increased sleep fragmentation. One study found that children with allergic rhinitis experienced ten times the number of arousals from sleep compared to children without nasal congestion [37, 38]. During the day, after experiencing poor sleep at night, these children are more fatigued than their peers and have worse school performance, some of which is postulated to be not only from poor sleep quality but also from the influence of the inflammatory mediators that cause the nasal congestion of allergic rhinitis [34, 39, 40].

The nasal congestion that occurs in allergic rhinitis can cause increased airway resistance and increased nasal collapse that can predispose to sleep-disordered breathing. Due to the nasal congestion, patients will often compensate with oral breathing which increases the risk for the airway collapse that can lead to obstructive sleep apnea. Oral breathing in children can also lead to so-called adenoid facies—retrognathia and high arched palate—which can exacerbate sleep apnea [41]. The prevalence of rhinitis and sleep apnea in children has not been well studied; however, adult studies have shown that those with allergic rhinitis were almost twice as likely to have moderate to severe sleep apnea [8, 42]. Rhinitis can also negatively impact patients with sleep apnea as those who have allergic rhinitis tend to experience more daytime sleepiness and fatigue than patients with sleep apnea alone [43]. Similarly, children with sleep apnea who are treated with an adenotonsillectomy do not experience as great improvements in quality of life if they have allergic rhinitis [44]. Thus, it is crucial to treat allergic rhinitis effectively and ensure that symptoms for allergic rhinitis are assessed appropriately. Adequate treatment of allergic rhinitis, often with nasal steroids, has been shown to improve both quality of sleep and daytime sleepiness [45]. Surgeons conducting adenotonsillectomy should consider the possibility of comorbid allergic rhinitis and treat aggressively to improve outcomes.

Atopic Dermatitis and Sleep

Of the three main allergic diseases, atopic dermatitis is the least studied in relation to sleep. However, providers who care for children with atopic dermatitis can attest to the profound impact that it has on sleep. About 60% of children with atopic dermatitis experience sleep disturbance at baseline; however, when undergoing an exacerbation, this number worsens to 83% of children [46]. Atopic dermatitis can cause severe skin itching that leads to difficulty falling asleep and sleep disruption throughout the night [47]. Actigraphy studies have shown that children and adults with atopic dermatitis have nearly twice as many wrist movements overnight associated with scratching compared to patients without atopic dermatitis. This then leads to sleep fragmentation and worse sleep efficiency on a nightly basis [48–50]. The link between atopic dermatitis and sleep-disordered breathing is less clear; however, frequent snoring is known to be more common in children with atopic dermatitis [51].

Assessing for Allergy and Sleep Disorders

Given the significant interplay between atopy and sleep, it is imperative that these children's medical providers do a thorough evaluation to determine if atopy and sleep are independently contributing to their condition. As with any medical assessment, a thorough history and physical exam is required. For patients with allergic complaints, it is recommended to ask about sleep and snoring at every visit. Unfortunately, the symptoms that patients with sleep disorders present with are

broad. Children can be excessively sleepy or can be hyperactive. They may have mood swings or may struggle with mood disorders. They may snore, mouth breath, or move an excessive amount at night. Given the myriad of symptoms associated with sleep disorders, it is often prudent to use a simple screening tool. The BEARS questionnaire was originally created for use in primary care clinics and is a quick and simple way to screen for sleep disorders (see Table 7.1). It consists of five different sections that each assess for a different element of sleep: *B*edtime problems, *E*xcessive daytime sleepiness, *A*wakenings during the night, *R*egularity and duration of sleep, and *S*leep-disordered breathing. It is broken down into three different

Table 7.1 BEARS sleep screening algorithm: Examples of developmentally appropriate trigger questions

	Toddler/preschool (2–5 years)	School-aged (6–12 years)	Adolescent (13–18 years)
1. **B**edtime problems	Does your child have any problems going to bed? Falling asleep?	Does your child have any problems at bedtime? (P) Do you have any problems going to bed? (C)	Do you have any problems falling asleep at bedtime? (C)
2. **E**xcessive daytime sleepiness	Does your child seem overtired or sleepy a lot during the day? Does she still take naps?	Does your child have difficulty waking in the morning, seem sleepy during the day, or take haps? (P) Do you feel tired a lot? (C)	Do you feel sleep a lot during the day? In school? While driving? (C)
3. **A**wakenings during the night	Does your child wake up a lot at night?	Does your child seem to wake up a lot at night? Any sleepwalking or nightmares? (P) Do you wake up a lot at night? Have trouble getting back to sleep? (C)	Do you wake up a lot at night? Have trouble getting back to sleep? (C)
4. **R**egularity and duration of sleep	Does your child have a regular bedtime and wake time? What are they?	What time does your child go to bed and get up on school days? Weekends? Do you think he/she is getting enough sleep? (P)	What time do you usually go to bed on school nights? Weekends? How much sleep do you usually get? (C)
5. **S**noring	Does your child snore a lot or have difficulty breathing at night?	Does your child have loud or nightly snoring or any breathing difficulties at night? (P)	Does your teenager snore loudly or nightly? (P)

From Mindell and Owens [55], with permission
The "BEARS" instrument is divided into five major sleep domains, providing a comprehensive screen for the major sleep disorders affecting children in the 2- to 18-year-old range. Each sleep domain has a set of age-appropriate "trigger questions" for use in the clinical interview
B = Bedtime problems
E = Excessive daytime sleepiness
A = Awakenings during the night
R = Regularity and duration of sleep
S = Snoring
(P) Parent-directed question
(C) Child-directed question

age ranges, preschool, school age, and adolescent with age-appropriate screening questions, and provides an excellent quick screen to be able to assess for sleep disturbances [52]. There are other questionnaires that may be used to assess specifically for sleep-disordered breathing such as the Pediatric Sleep Questionnaire (PSQ-22) [53] and Obstructive Sleep Apnea (OSA-18) [54]; however, for a non-sleep physician, the BEARS questionnaire is a concise and comprehensive screening tool for sleep. Positive answers should trigger further history gathering and a referral to a pediatric sleep specialist for further management and treatment if indicated.

For providers seeing patients with sleep complaints, it is crucial to determine if these issues may be associated with or worsened by an allergic disorder. The symptoms of allergic disorders are broad, and unfortunately there are few concise and comprehensive screening tools available [4]. Thus, a thorough history that addresses asthma, allergic rhinitis, and atopic dermatitis should be done. Common symptoms of asthma include wheezing, shortness of breath, and cough. Allergic rhinitis can be assessed for by inquiring about nasal congestion and runny nose. Atopic dermatitis often manifests with persistent itching. A targeted physical exam can be revealing, as well. Children with asthma will often manifest with wheezing, especially on forced exhalation. Allergic rhinitis presents as clear rhinitis with boggy nasal mucosa. Atopic dermatitis (eczema) typically presents as red, dry, hypertrophied skin on the flexor surfaces of the limbs. In general, children with allergic disease may present with Dennie-Morgan folds, allergic shiners, and an allergic crease on the nose. If these physical findings are present and a positive history is obtained, further evaluation should be considered. However, non-specific testing by the sleep medicine doctor is not recommended. False-positive "allergy" testing can be as high as 50%. Initial empiric treatment for allergic disease by the sleep medicine physician is reasonable, such as antihistamine for allergic rhinitis. However, if not adequately responsive or if the condition is not clear, it is best to refer to an allergist for detailed evaluation and management. A differential diagnosis of these common allergic conditions can include more ominous conditions, so referral is prudent when presenting symptoms are not typical.

Conclusions

Allergy and sleep disorders co-contribute to "each other's" morbidity. It is crucial to recognize that asthma, allergic rhinitis, and atopic dermatitis can worsen sleep and quality of life. The former two are also associated with sleep-disordered breathing. Sleep-disordered breathing, in turn, can worsen control of asthma. There is a growing body of evidence that these disorders may impact neurobehavioral and psychological outcomes; thus, it is crucial that appropriate screening tools, history taking, and physical exams are performed in all children that present with these disorders.

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Evaluation and Management of a Sleepy Child

8

Anne Marie Morse and Sanjeev V. Kothare

Children with atopic diseases, such asthma or allergic rhinitis, are particularly vulnerable to sleep dysfunction and resultant excessive daytime sleepiness (EDS) [1]. Sleep is a homeostatic process that is important for normal growth and development in children. About 20–30% of children, on average, have difficulties initiating and/or maintaining sleep [2]. These difficulties can be persistent, transient, and reoccurring. Children with allergic disease are more likely to have comorbid sleep difficulties and excessive daytime sleepiness [3, 4]. In fact, the more severe the allergic illness and the poorer the control of allergy symptoms, the greater the likelihood for sleep pathology [5]. The most commonly considered category of sleep disorders in patients with allergic disease is sleep-disordered breathing. This is because upper and lower airway resistance is commonly found in these patients and can increase the risk for sleep-disordered breathing events. However, it is important to recognize that there are additional causes to consider, which can produce symptoms of EDS. A detailed evaluation to determine correct etiology for EDS is necessary.

Clinical Presentation of Excessive Daytime Sleepiness in a Child

Excessive daytime sleepiness is defined as an increased tendency to fall asleep in a setting that an individual would be expected to stay awake and alert. Identification of sleepiness in a child requires an understanding of age-specific sleep patterns and

A. M. Morse
Department of Child Neurology, Sleep Medicine, Geisinger Medical Center, Janet Weis Children's Hospital, Danville, PA, USA

S. V. Kothare (✉)
Pediatric Sleep Program, Department of Neurology, NYU Langone Medical Center, New York, NY, USA
e-mail: skothare@northwell.edu

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Table 8.1 Sleep hours and patterns by age

Stage	Age	Average sleep need (h)	Minimum sleep need (h)	Maximum sleep need (h)	Sleep pattern over 24 h
Newborn	0–3 months	14–17	11–13	18–19	Several short day naps *(minutes up to 1–2 h)* Long night sleep *(several hours at a time with waking for feeding)*
Infant	4–11 months	12–15	10–11	16–18	Several short day naps *(minutes up to 1–2 h; Reduced number and length of naps)* Long night sleep *(waking for feeding; increased time between feedings; may sleep entire night)*
Toddler	1–2 years	11–14	9–10	15–16	1–2 day naps *(reduced number and length of naps)* Long night sleep *(may sleep entire night, but waking 1-2x for feeding can be normal)*
Preschool	3–5 years	10–13	8–9	14	Decreased to no day naps *(occasional napping still normal)* Consolidated night time sleep
Preteen	6–13 years	9–10	7–8	12	Consolidated night time sleep
Teenager	14–17 years	8–10	7	11	Consolidated night time sleep *(may have delayed sleep onset)*

durations (Table 8.1). Clinical features that may suggest symptoms of excessive daytime sleepiness include (a) increased nocturnal sleep duration for age, (b) napping that is inconsistent with age, (c) appearing sleepy when age equivalent peers are awake, and alert (d) an increased sleep need compared to patient's previous needs. Children with excessive daytime sleepiness can sometimes be difficult to identify. It is not uncommon for a child to manifest with symptoms of inattention and hyperactivity, suggestive of attention-deficit hyperactivity disorder, as a presentation of insufficient sleep or sleep-wake dysfunction [6]. In this scenario, the child may doze when forced to be sedentary or restricted in activity.

Causes of Excessive Daytime Sleepiness

There are numerous causes of excessive daytime sleepiness. It is helpful to consider the possible causes of sleepiness as a result of three main categories, insufficient sleep, fragmented sleep, and increased sleep drive, to improve identification of etiology of symptoms (Table 8.2). An accurate identification of cause is critical for appropriate intervention to improve symptoms of sleepiness.

Table 8.2 Causes of excessive daytime sleepiness

Increased need of sleep	Insufficient sleep	Fragmented sleep
Narcolepsy Type 1 Type 2 Idiopathic hypersomnia Kleine-Levin syndrome Genetic syndromes Neurologic disorders Head trauma Hypothalamic lesions (craniopharyngioma, demyelinating, degenerative, infectious, astrocytoma, vascular) Increase intracranial pressure Transient hypersomnia Medical disorders Infection Metabolic Endocrine Psychiatric Drug induced (medications, illicit drugs)	Insomnia Behavioral insomnia of childhood Sleep initiation Sleep maintenance Due to medications, alcohol, drugs Due to medical/psychiatric disorders Idiopathic Circadian rhythm disorder Delayed sleep phase Non-24 h Abnormal sleep entrainment (development delay/intellectual disability)	Medical disorders Atopy (asthma, eczema, allergies) Gastroesophageal reflux Epilepsy Environmental Noise, light, temperature, pets Behavioral disorders Sleep-related breathing disorders OSA UARS Hypoventilation Central sleep apnea Sleep-associated movement disorders PLMD RLS Bruxism Jactatio capitis nocturna (head banging), body rocking Parasomnias Night terrors Sleep walking Sleep talking Confusional arousals REM behavior disorder Nightmare disorders

Association Between Sleep and Allergic Disease

There is an intimate relationship between allergic disease and sleep. Clinical guidelines that evaluate illness-related morbidity in allergic disease identify symptom induced sleep loss as an important clinical factor in determination of severity of allergic disease [7]. In other words, symptoms of excessive daytime sleepiness and poor sleep quality can serve as a surrogate indicator of poor control of allergic disease [8]. Asthma and allergic diseases can influence sleep through several factors, such as inflammatory mediators in poorly controlled disease, poor trigger control in the home, and side effects of medication or nonadherence to medications.

Table 8.3 Sleep history

Document sleep-wake patterns for weekdays and weekends (include bedtime, wake time, any variations, frequency, and duration of any naps)
Evaluate frequency, duration, severity, development, and fluctuations of nighttime sleep difficulties or reported daytime sleepiness
Assess possible contributing factors (e.g., pain, environmental factors, and comorbid psychiatric and medical conditions)
Evaluate for effects of sleep-wake disturbances (e.g., fatigue, sleepiness, mood, cognition, physical functioning)
Document use of medication and other substances (e.g., natural products, caffeine, alcohol, or recreational drugs)
Evaluate for symptoms of specific sleep disorders (e.g., snoring, apneas, sleep-related hallucinations, nightmares, limb movements)

Approach to the Evaluation of a Sleepy Child

History

An intake detailing the child's sleep-wake history and pattern (Table 8.3) is a critical part of identifying the cause of excessive daytime sleepiness. The sleep history may be obtained by the parent, child, or combination of both. In some circumstances, such as when the child is in daycare or with another care provider, there is a need to obtain history, regarding napping and wakefulness behavior, from these sources as well. A detailed sleep-wake history should be performed in all patients to determine if there are features concerning for a sleep disorder. If there are continued complaints of sleepiness, patients should be re-evaluated for sleep-wake dysfunction symptoms.

Past medical and surgical histories may provide indication of being higher risk for some sleep disorders, such as iron deficiency anemia and restless leg syndrome or tonsillectomy for recurrent pharyngitis and sleep-disordered breathing. Family medical history evaluation for sleep disorders should be elicited. Deteriorating school performance may also suggest an underlying sleep disturbance, as there has been suggestion that sleep disturbances can cause prefrontal cortical dysfunction with impaired executive functioning leading to daytime cognitive and behavioral difficulties in children [9].

Subjective Assessments

Validated sleep questionnaires can supplement the history obtained by the provider. In some cases, it can aid in expediting identification of the cause of EDS (Table 8.4). On the other hand, scales dedicated to the quantification of sleepiness can be used as a method of classifying severity and monitoring subjective improvement with treatment (Table 8.5).

Table 8.4 Diagnosis specific questionnaires

Scale	Swiss Narcolepsy Scale	CH-RLSq	BEARS
Description	Assesses for five symptoms that can be used to screen for the presence of narcolepsy with cataplexy	Self-completed questionnaire consisting of 13 questions that probe the 4 basic criteria of RLS as well as mimics of RLS	Screening tool to quickly assess for risk factors for various sleep disorders
Questions	1. How often are you unable to fall asleep? 2. How often do you feel bad or not well rested in the morning? 3. How often do you take a nap during the day? 4. How often have you experienced weak knees/ buckling of the knees during emotions like laughing, happiness, or anger? 5. How often have you experienced sagging of the jaw during emotions like laughing, happiness, or anger?.	1. Do you have, or have you had, recurrent uncomfortable feelings or sensations in your legs while you are sitting or lying down? 2. Do you, or have you had, a recurrent need or urge to move your legs while you were sitting or lying down? 3. Are you more likely to have these feelings when you are resting (either sitting or lying down) or when you are physically active? 4. Do these feelings usually start when you are resting (either sitting or lying down)? 5. If you get up or move around when you have these feelings, do these feelings get any better while you actually keep moving? 6. Which times of day are these feelings in your legs most likely to occur? 7. Which times of day are these feelings in your legs least likely to occur? 8. Will simply changing leg position by itself once without continuing to move usually relieve these feelings? 9. Are these feelings ever due to muscle cramps?b. If so, are they always due to muscle cramps? 10. Do these feelings occur only when sitting or only when lying down? 11. When you actually experience the feelings in your legs, how distressing are they? 12. In the past 12 months, how often did you experience these feelings in your legs? 13. Approximately how old were you when you first noticed these feelings in your legs?.	1. Do you have any problems falling asleep at bedtime? 2. Do you feel sleepy a lot during the day? In school? While driving? 3. Do you wake up a lot at night? 4. What time do you usually go to bed on school nights? On weekends? How much sleep do you usually get? 5. Parent: Does your child snore loudly? Child: Has anyone told you that you snore loudly at night?.

(continued)

Table 8.4 (continued)

Scale	Swiss Narcolepsy Scale	CH-RLSq	BEARS
Scoring	(Scored using the weighted formula: 6xQ1 + 9xQ2 - 5xQ3 - 11xQ4 - 13xQ5 + 20) A score of <0 is suggestive of narcolepsy with cataplexy	Definite RLS: 1 yes, 2 yes, 3 resting, 4 yes, 5 NOT equal or morning, 6 does not usually relieve, 7 a as no OR b as no.	Yes responses are high risk for sleep disorder; bed routine response subjective and age specific

From Refs. [25, 30–32]
CH-RLSq Cambridge Hopkins Restless Leg Syndrome Questionnaire
*BEARS B*edtime problems, *E*xcessive daytime sleepiness, *A*wakenings during the night, *R*egularity and duration of sleep, *S*leep-disordered breathing

Table 8.5 Sleepiness scales

Scale	Epworth Sleepiness Scale (ESS)	ESS-CHAD	Pediatric Daytime Sleepiness Scale
Questions	*Rate likelihood to doze* 1. Sitting and reading 2. Watching TV 3. Sitting inactive in a public place (e.g., theater/meeting) 4. As a passenger in the car for an hour without break 5. Sitting and talking with someone 6. After lunch without alcohol 7. While stopped for a few minutes in traffic	*Rate likelihood to doze* 1. Sitting and reading 2. Watching TV 3. Sitting inactive in a public place (e.g., movies/class) 4. As a passenger in the car for an hour without break 5. Sitting and talking with someone 6. After lunch 7. Taking a test/doing homework	1. How often do you fall asleep or get drowsy during class? 2. How often do you get sleep or drowsy while doing your homework? 3. Are you usually alert most of the day? 4. How often are you ever tired and grumpy during the day? 5. How often do you have trouble getting out of bed in the morning? 6. How often do you fall back to sleep after being awakened in the morning? 7. How often do you need someone to awaken you in the morning? 8. How often do you think you need more sleep?
Scoring	Responses: Never =0, rarely = 1, sometimes = 2, almost always = 3	Responses: Never =0, rarely = 1, sometimes = 2, almost always = 3	Responses: Never = 0, seldom = 1, sometimes = 2, often = 3, always = 4
TOTAL	Total score ≥ 10 indicates sleepiness	Total score ≥ 10 indicates sleepiness	Normal <15; > 20 indicates sleepiness

From Refs. [33–35]
ESS-CHAD Epworth Sleepiness Scale for Children and Adolescents

Physical Examination

The physical exam may identify clinical features that suggest increase susceptibility for sleep-wake disorders. Review of vital signs can provide direction as to whether there is a more systemic concern present. The general evaluation provides some sense of the severity of sleepiness (i.e., patient actively sleeping or difficult to stay awake versus hyperactive and impulsive), overall health, and body habitus. There is a strong association between OSAS in older children and adolescents; however, only a modest association has been identified in young children who are overweight [10]. The head, eyes, ears, nose, and throat exam can identify anatomy that may increase risk for airway collapse. Allergic shiners, enlarged boggy turbinates, and tonsillar hypertrophy are common findings in patients with allergies that can increase nasal resistance leading to increased negative pressure swings and resultant pharyngeal collapse. Mallampati score and tonsillar size have been identified as independent predictors of OSA [11]. Congenital craniofacial abnormalities, such as cleft lip/palate, high-arched palate, micrognathia, and retrognathia should also be considered as risk factors for a more vulnerable narrow airway.

Investigations to Consider

If there is suggestion of a sleep disorder, the physician may require the patient to maintain a sleep diary, wear a sleep tracking device called an actigraphy, or have a polysomnography (PSG) performed. The suspected etiology of sleep disorder dictates which assessment is most appropriate.

Sleep Diary

A sleep diary is a record of a patient's sleep patterns and habits. The data recorded includes information about the sleep itself: bedtime, sleep latency, waking time, number of arousals, as well as about factors that may influence sleep and wake, such as activities within 1 h of bed, caffeine and alcohol intake, exercise duration and timing, and medications taken. In a young child, these are completed by the parent, and in an older child, self-report can be used. However, if possible, input from both the child and the parent may be most useful.

Actigraphy

Actigraphs are typically watch-like devices, generally worn on the non-dominant wrist, that estimate sleep-wake cycle based on movement. Active movement registers as wakefulness and lack of movement as sleep. The American Academy of Sleep Medicine recognizes actigraphy as a low-cost noninvasive method for screening of sleep disorders, especially sleep-wake cycle disorders, such as insomnia or

circadian rhythm disorder. The sleep parameters that can be estimated using this device include sleep duration, sleep efficiency, and waking time after initial sleep onset. Sleep diaries are frequently used in combination with actigraphy to increase the yield of additional factors that may be relevant to the sleep-wake patterns seen, such as caffeine use and timing, bedtimes, and patient's perception of being awake or sleep [12].

Fitness Trackers

Wearable fitness-tracker devices have become quite popular, with almost all of them having some form of sleep-wake tracking software. The majority of these devices have a similar mechanism for tracking sleep-wake cycles as the medically used actigraphs. The low-cost, wide availability, and patient interest in the use of these devices make them a considerable alternative to standard actigraphy to gauge daily sleep-wake rhythms. However, there is limited data demonstrating consistent results using these devices making their use in clinical practice questionable [13–15].

Polysomnography (PSG)

A polysomnography is most commonly used to evaluate patients who are high risk for sleep apnea, which many patients with allergy may be at risk for. However, it is also used to evaluate for other types of sleep disorders, such as parasomnias or refractory insomnia. A routine sleep study uses a limited EEG to record brain waves to stage sleep, a nasal cannula device to evaluate breathing through the nose and mouth, a pulse oximeter on the finger to measure oxygen levels, a belt around the chest and abdomen to evaluate breathing, and leads to evaluate heart rate and rhythm, eyes leads and leg movements during the study. If there is concern for seizure, extra EEG and body leads may be used to better assess brain activity and body movements. In general, home sleep studies are not appropriate for pediatric patients, as there is frequently excessive artifact that limits interpretation.

Multiple Sleep Latency Test (MSLT)

Children with symptoms of excessive daytime sleepiness may be evaluated with additional testing, in addition to polysomnography, such as a multiple sleep latency test (MSLT) or maintenance of wakefulness test (MWT). Sleep logs may be completed for at least 2 weeks prior to the study, to evaluate for contribution of chronic sleep insufficiency or a circadian rhythm disorder. The MSLT occurs on the day following an overnight polysomnography. The patient has four to five opportunities to nap, with each opportunity lasting 20 min and separated by 2 h. The goal of this testing is to determine severity of sleepiness. This is done by obtaining the average time taken to fall asleep (sleep latency) and also evaluate if they achieve REM sleep

after a full night's rest (sleep-onset REM period – SOREMP). In general, it takes about 90–120 min to cycle into REM sleep, so entering REM sleep during a 20-min nap is considered pathologic.

MWT

Maintenance of wakefulness testing evaluates the ability to stay awake and generally is used to determine if interventions to treat daytime sleepiness are successful. The test consists of four trials lasting about 40 min each trial with a 2-h break between each trial. For each trial, the patient sits quietly in bed in a dimly lit room with his back and head supported by a pillow. The goal is to try to stay awake for as long as you can while maintaining that position.

Common Sleep Disorders

Insomnia

Insomnia is defined as either difficulty falling asleep, staying asleep, or both and results in decreased number of hours of sleep, resulting in a sense of sleeplessness in the night and sleepiness in the day. Symptoms of insomnia can be acute, chronic, or recurring. In younger children, the most common cause is behavioral insomnia of childhood (BIC). BIC is classified into three categories: sleep-onset association type, limit-setting type, and combined type. With sleep-onset association type, the child makes a connection between falling asleep and other factors, such as a location (parents bed) or activity (breast/bottle feeding), which can interfere with initiating sleep if these factors are not present. In limit-setting type, the child either refuses, requests, or makes excuses to avoid a set bedtime, and parents don't respond with consistent limitations, resulting in delayed bedtime. Combined type has features of both. It is also important to identify if sleep scheduling or inappropriate napping is contributing to sleep difficulties, such as putting a child to bed too early or napping outside of developmental need (Table 8.1).

Older children and teenagers, who have difficulty falling asleep, generally have poor sleep habits, including variable sleep schedules, later bedtime, and daytime napping, that are causative. It is important, especially in adolescents, to distinguish insomnia symptoms from a circadian rhythm disorder as this will impact approach to treatment.

Circadian Rhythm Sleep Disorders

Circadian rhythm sleep disorders (CRSDs) are chronic sleep-wake rhythm disturbances that result from a misalignment between the timing of an individual's biologic circadian rhythm and the sleep-wake times required by exogenous factors,

such as school schedules. Delayed sleep phase syndrome (DSPS) is the most common sleep disturbance seen in adolescents. This is due to a physiological shift in melatonin production resulting in later timing sleep onset in the night. This is frequently mistaken for sleep initiation insomnia, as there the patient also has difficulty falling asleep at their desired bedtime and an inability to wake spontaneously at the desired time in the morning. The difference is when the exogenous factors are removed in a DSPS, sleep duration and quality is age appropriate and refreshing, but not in insomnia. During school days, the delayed bedtime and sleep-onset combined with earlier waking time results in reduced sleep duration, chronic sleep deprivation, and excessive daytime sleepiness.

Additional factors that can contribute to the development of both insomnia and DSPS include illicit substance, caffeine, and nicotine use. In addition, undiagnosed symptoms of depression or anxiety can contribute to difficulty falling and staying asleep. Excessive screen time, as in watching TV, cell phone, and computer use, especially close to bedtime, can interfere with falling asleep. The activity itself may be stimulating, but also the light emitted, specifically the wavelength of blue light (475 nm), causes a delay in endogenous melatonin production delaying sleep onset [16].

Sleep-Disordered Breathing

Sleep-disordered breathing includes upper airway resistance syndrome, obstructive sleep apnea, central sleep apnea, and hypoventilation syndromes. Obstructive sleep apnea (OSA) is the most common form of sleep-disordered breathing and carries a higher prevalence in allergic patients. OSA is characterized by transient episodes of breathing difficulty because of obstruction in the upper airway. Pediatric sleep apnea is diagnosed with a polysomnography that demonstrates an apnea hypopnea index (AHI) of more than 1.5 or an apnea index (AI) of more than 1. Severity of sleep apnea is determined by AHI: mild OSA, AHI 1.5–5; moderate OSA, AHI 5–10; and severe OSA, AHI greater than 10. This differs from the adult values for determining severity: mild OSA, AHI 5–15; moderate OSA. AHI 15–30; and severe OSA, AHI greater than 30. In younger children, sleep apnea is commonly related to enlarged tonsils, adenoids, or craniofacial features, such as a micrognathia or flattened nasal bridge/facial features, which physically reduces the size of the airway. As described earlier, an overweight body habitus can contribute to risk of developing symptoms and has been increasing in frequency as a contributing factor. On the other hand, it is not uncommon for a child with sleep-disordered breathing to have failure to thrive characteristics [17]. Individuals who have obstructive sleep apnea commonly have the following signs and symptoms: snoring, open mouth breathing, episodes of stopping breathing (apnea), episodes of difficulty breathing (hypopnea), and frequent arousals during sleep. There may also be symptoms of increased nocturnal urination or bedwetting, morning headache, restless sleep, morning thirst, excessive daytime sleepiness, and cognitive slowing.

Upper airway resistance syndrome frequently has features similar to obstructive sleep apnea. In fact, UARS is included under the diagnosis of OSA by the American Academy of Sleep Medicine [18]. There is no diagnostic criterion defined for UARS. However, UARS is suspected in patients who have excessive daytime sleepiness, do not have OSA, but do have evidence of increased upper airway resistance, such as flow limitation during sleep on PSG [19].

Children with either central sleep apnea or hypoventilation symptoms frequently lack the symptoms commonly seen in OSA or UARS. Central apnea can occur independently and comorbid to obstructive events. Central apnea is the result of failure of the respiratory center to trigger a breath. When central apnea is predominant, there should be consideration for evaluating for structural brain pathology, as well as pulmonary, cardiac, or renal dysfunction that may cause these events. Medications should also be reviewed as some, such as opiates, barbiturates, and benzodiazepines, can induce central events.

Periodic Limb Movement Disorders

Periodic limb movement disorders (PLMD) are repetitive movements, typically in the lower extremities, that occur about every 20–40 s during sleep. Parents may describe witnessed episodes, or the patient may describe experiencing frequent movements, described as brief muscle twitches, jerking movements, or an upward flexing of the feet that may cluster into episodes that last from minutes to several hours. These events may disrupt sleep because of arousals resulting from these movements. Restless leg syndrome (RLS) is a subcategory within periodic limb movement disorders. There is evidence of PLMD that is associated with an uncomfortable sensation in the calves or thighs that may interfere with falling asleep or during an arousal. It can be challenging to make the diagnosis of RLS in younger children because of limitations in their ability to describe their symptoms [20]. Supportive evidence such as the presence of PLMS on PSG or family history of RLS may be helpful for diagnosis in children. The International Restless Legs Study Group has published a set of proposed consensus criteria for reaching the diagnosis of RLS and PLMD in pediatric populations [21].

Parasomnias

Parasomnias are disorders of arousal that are characterized by abnormal or unusual behavior during sleep. There are NREM and REM parasomnias (Table 8.6). NREM parasomnias typically occur when a patient has an arousal during slow-wave sleep (stage N3), and REM parasomnias occur when the arousal comes out of REM sleep. NREM parasomnias are more common during early childhood and become less frequent with age. REM parasomnias more commonly occur in adults and can worsen with age. If a REM parasomnia is present in a child or adolescent, it is likely related to neurodevelopmental disorder, medication side effect, or undiagnosed

Table 8.6 Parasomnias

	Sleepwalking/sleep talking	Confusional arousals	Sleep terror	Nightmares	REM behavior disorder
Timing during sleep	First third	First third	First third	Second half	Second half
Sleep stage	N3	N3	N3	REM	REM
Age group	Children	Children	Children	Children	Adults
Duration	2–30 min	5–40 min	1–10 min	3–20 min	Mins
Agitation	None/mild	Moderate	Significant	Mild	Non-significant
Autonomic changes	None/mild	Moderate	Severe	Mild	Severe

narcolepsy [22]. NREM parasomnia frequency can be increased in children with either chronic sleep deprivation or a comorbid sleep disorder. If a comorbid sleep disorder is present, this can increase arousals. Alternatively, sleep deprivation causes a rebound increase in time spent in stage N3 when the patient does fall asleep. In both instances, this increases the likelihood for a NREM parasomnia to occur.

Hypersomnias

The International Classification of Sleep Disorders third edition (ICSD3) of the American Academy of Sleep Medicine identifies the following hypersomnia disorders: central disorders of hypersomnolence, which include narcolepsy type 1 (previously narcolepsy with cataplexy) and narcolepsy type 2 (previously narcolepsy without cataplexy), idiopathic hypersomnia, Klein-Levin syndrome [23].

Narcolepsy type 1 is defined as excessive daytime sleepiness plus cataplexy and a positive MSLT. A positive MSLT is, based on the adult criteria, a mean sleep latency of less than 8 min and two SOREMPs. Alternatively, it can be identified by low CSF hypocretin levels; however, this testing is not commercially available. Narcolepsy type 2 is defined as excessive daytime sleepiness plus a positive MSLT, but there is no evidence of either cataplexy or low CSF hypocretin. Symptoms of narcolepsy include excessive daytime sleepiness, fragmented sleep due to sleep-wake instability, sleep paralysis, sleep-related hallucinations, and ± cataplexy. Cataplexy is transient episodes of loss of tone, which can be complete (generalized) or partial (focal), and is frequently provoked by strong emotion, typically laughter. Children are more likely to have partial cataplectic events, such as dropping items from hands, head drop or nod, or knees buckling, that may not be associated with strong emotion [24]. Although positive MSLT testing is part of the diagnostic criteria for the diagnosis of narcolepsy in children, normative data does not exist for children under the age of 8 years. At disease onset, symptoms may be unstable; therefore, children may require multiple MSLTs as their symptoms progress [25].

Idiopathic hypersomnia is chronic unexplained severe excessive daytime sleepiness with no evidence of another sleep disorder to cause the EDS. Idiopathic hypersomnia is qualified by having either a multiple sleep latency testing demonstrates a

reduced sleep latency of 8 min or less but has less than 2 SOREMPs or documentation of greater than 660 min in a 24-h period.

Kleine-Levin syndrome (KLS) is a rare disorder that generally has an onset in adolescence and is characterized by recurrent episodes of hypersomnia, which are often associated with hyperphagia and hypersexuality. The episodes of hypersomnia can last up to 10 days and can recur several times a year. In between the symptomatic periods, the patient will have normal sleep requirements with no symptoms of excessive daytime sleepiness. Males are more likely to be affected than females. However, when females are affected, they tend to have a more chronic course than males.

Approach to Treatment

Insomnia

Pediatric insomnia is best treated with behavioral interventions directed at improving sleep initiation and duration, resulting in increased total sleep time and improved sleep quality. There are various methods that can be used in younger children, which are summarized in Table 8.7. Regardless of method chosen, parental consistency is one of the most important factors for successful outcomes. These methods have been shown produce reliable and lasting improvements in bedtime problems and night wakings [26].

Table 8.7 Behavioral interventions for insomnia

Sleep training method	Description of intervention
Extinction (unmodified)	Reinforce sleep hygiene. Parent puts child to bed drowsy, but NOT asleep. Child has to learn to settle to sleep on his own. The *parent is not to respond to child's crying*
Gradual extinction	Reinforce sleep hygiene. Parent must *ignore disruptive bedtime behaviors for a predetermined period of time*. If the child has not settled at the end of that time, the parent settles the child back in bed but minimizes interaction with the child. Parents follow this procedure for at least 1 week and then follow an unmodified extinction procedure
Faded bedtime	First, determine time child is likely to fall asleep in 15 min. Reinforce sleep hygiene. *Once the child falls asleep at this time with little resistance, the bedtime is set earlier*. Once the new bedtime is successful for at least 1 week, then it can be moved earlier again. Wake time is set at the same time each day, and the child is not allowed to sleep outside the prescribed sleep times
Limit setting	*Develop realistic and consistent bedtime rules*. Reinforce sleep hygiene Limit number of times the child can make a request to stay awake/out of bed Limit how late other activities, such as watching TV, gaming, or internet time
Cognitive behavioral therapy	Counseling directed at *changing actions and/or thoughts that interfere with falling and staying asleep* through a combination of strategies including sleep hygiene, stimulus control, sleep restriction if needed, relaxation training/biofeedback, and cognitive control and psychotherapy

From Refs. [36, 37]

For older children and adolescents, behavioral interventions are generally, at least initially, directed at reducing arousal at bedtime. Practicing good sleep hygiene and maintaining a regular sleep schedule are basic treatment principles. Sleep hygiene education (Table 8.8) provides guidance to develop habits that will impact the initiation and maintenance of sleep. A regular sleep schedule, 7 days a week, allows for sleep inertia to build enough during the day that by evening the patient is ready to sleep. Cognitive behavioral therapy for insomnia (CBT-I) may also be used for patients with poor sleep habits, difficult sleep schedules, and challenging views on insomnia. CBT-I has been shown to be more effective than any of the leading sedatives or hypnotics for long-term insomnia treatment. These medications include benzodiazepines, antidepressants, melatonin, melatonin-receptor agonists, and non-benzodiazepine receptor agonists (Table 8.9). Consideration for a patient's sleep comorbidities is important, as some medications can worsen other sleep disorders, such as restless leg syndrome or sleep-disordered breathing.

Table 8.8 Sleep hygiene tips for children and adolescents

1. Sleep only as much as you need to feel refreshed during the following day
2. Get up at the same time each day, 7 days a week
3. Exercise regularly
4. Make sure your bedroom is comfortable and free from light and noise
5. Make the bedroom a safe, inviting place to sleep
6. The bed is only for sleeping
7. Make sure that your bedroom is at a comfortable temperature during the night
8. Eat regular meals and do not go to bed hungry
9. Avoid excessive liquids in the evening
10. Cut down on all caffeine products and no caffeine after lunch
11. Don't take your problems to bed
12. Do not *try* to fall asleep
13. Put the clock under the bed or turn it so that you can't see it
14. Avoid naps

Table 8.9 Medications to treat pediatric insomnia

Medication class	Medications	Notes
Alpha-agonists	Clonidine Guanfacine	Guanfacine is less sedating/less anticholinergic side effects than clonidine consider use in comorbid ADHD
Melatonin and receptor agonists	Melatonin Ramelteon	Melatonin may be helpful but is frequently more useful in CRD Ramelteon has limited data in children
Antihistamines	Diphenhydramine Hydroxyzine	Tolerance frequently develops requiring escalating doses Caution of higher dose causing anticholinergic side effects
Benzodiazepines	Clonazepam	Consider use in comorbid parasomnia, PLMD Can worse SDB
Antidepressants	TCAs (amitriptyline, nortriptyline) Trazadone	Obtain EKG Consider use in comorbid depression/ anxiety

Circadian Rhythm Disorders

Delayed sleep phase syndrome is frequently corrected using melatonin. Melatonin can have either chronobiologic or hypnotic effects. Lower doses, 0.3–3 mg, given 2–3 h prior to corrected bedtime may aid in resetting the delay sleep phase [27]. Frequently, this is recommended in combination with exposure to bright light in the mornings after awakening for at least 15–20 min.

Sleep-Disordered Breathing

Otolaryngology referral for evaluation for surgical intervention, such as adenotonsillectomy, is considered first line for children with OSA, as adenotonsillar enlargement is a common cause, especially in allergy patients. Children with craniofacial disproportion (e.g., micrognathia, retrognathia, high-arched palate) may benefit from surgical intervention to correct the disproportion. For children and adolescents where there is no surgically modifiable option or there is residual sleep-disordered breathing despite surgery, a continuous positive airway pressure device (CPAP) is prescribed. Patients with hypotonia may have a significant sleep positioning component to their breathing difficulty (i.e., worsening in supine sleep), and therefore sleep positioning may provide some benefit. Sleep positioning provides little to no benefit if there is fixed obstruction, such as adenoid and tonsillar enlargement.

Central sleep apnea is generally treated with either a positive airway pressure device, supplemental oxygen, or in some cases both. In some instances, the use of medications, such as caffeine, theophylline, and acetazolamide, is used to stimulate breathing. If there is an underlying medical cause, this needs to be addressed.

Periodic Limb Movement Disorder and Restless Leg Syndrome

Periodic limb movement disorder can occur incidentally (without identified cause) or as a result of some medications. A complete blood count and iron and ferritin levels should be evaluated, as anemia, iron deficiency, or a ferritin level less than 50 mcg/L may provoke symptoms of PLMD. Iron supplementation, generally 1–3 mg/kg/day of ferrous sulfate, is frequently recommended for at least 3 months, if no contraindications to its use exist. Co-administration with vitamin C or orange juice is recommended for improved iron absorption. If iron supplementation is not optimal, either due to contraindication or lack of efficacy, other medications, such as clonidine, gabapentin, clonazepam, and benzodiazepine, can be considered, but controlled trials in children are lacking. If a medication is suspected to be the precipitating factor, removing it can be both diagnostic and therapeutic for the child.

Parasomnias

Parasomnia treatment is generally directed at behavioral management and safety measures. Sleep hygiene and avoiding sleep deprivation is primary. Scheduled awakenings prior to the typical time of onset of the parasomnia can reduce the occurrence of events. However, parents should be educated not to try to wake the child during the event as this can aggravate the symptoms. If there is a comorbid sleep disorder, it should be treated. In the setting of severe cases of parasomnia or if there is high risk for injury, benzodiazepines, alpha-agonists, or melatonin can be used [28].

Hypersomnias

The approach to treatment for all of the hypersomnia disorders is similar, as there is no evidence that therapeutic response is substantially different for hypersomnia disorders with or without SOREMPs on the MSLT [29]. Pharmacologic intervention typically is either wake-promoting agents, such as modafinil and armodafinil, or stimulant medication, such as amphetamines and methylphenidate. Sodium oxybate is also an effective medication for treatment of excessive daytime sleepiness but is typically reserved for use only in children with narcolepsy type 1. Behavioral strategies, such as strategic and scheduled napping, are helpful to further reduce symptoms. Any child with severe excessive daytime sleepiness, related to hypersomnia or another sleep disorder, is eligible for a 504 plan in school, which can provide the child with accommodations to compensate for sleepiness symptoms so that he is not compromised academically.

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Evaluation and Management of the Sleepless Child

9

Rafael Pelayo

"The baby won't sleep," "My child won't sleep," and "I can't sleep" are complaints every healthcare provider working with sleep disorders will routinely need to address. As a clinician what goes through your mind when you hear these complaints? Do you look forward to working with patients with these complaints? There are many reasons an infant, young child, or adolescent may be considered sleepless. Allergies may be an overlooked reason for sleeplessness and may also be an exacerbating factor. This chapter will provide a clinical framework to understand what leads to sleeplessness in order to reach a diagnosis and treatment plan for children of all ages. Once a diagnosis is reached, then a rational approach to a treatment plan the family can understand and follow can be developed. The temptation to jump to treatment before understanding the root cause of the sleep problem needs to be avoided if long-term success is the goal.

At the immediate start of the clinical encounter, parents may ask "what can you give my child" or say their child "will not sleep" unless something is prescribed. If the patient is an adolescent at the onset of the initial visit, it must be determined if the adolescent thinks help is needed or is being forced to be there by a parent. Taking a large step back and getting a more comprehensive history are necessary before discussing any medication options. How large a step back? The clinician should keep in mind that most sleep disorders have a familial component. For example, obstructive sleep apnea runs in families, as do parasomnias such as sleepwalking. So before asking too many details about how the child is sleeping, first ask about how the parents themselves are sleeping. It is especially important to learn about how they slept *before* they were parents. One of the adults may have had a prior history of insomnia that has sensitized them to the normal awakenings of an infant. For example, a parent of a 3-month-old infant may complain the baby wakes

R. Pelayo (✉)
Department of Psychiatry and Behavioral Sciences, Stanford Center for Sleep Sciences and Medicine, Stanford Sleep Medicine Center, Redwood City, CA, USA
e-mail: pelayo@stanford.edu

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up twice a night. Upon questioning they tell you the child falls asleep fairly quickly after eating. An infant with only two brief awakenings to feed would not ordinarily be considered pathological in this age group. However, the parent may say, “the problem is I can’t fall asleep afterwards.” In that situation who has the sleep disorder, the parent, the infant, or both? It is not uncommon for people that have trouble sleeping to sometimes blame themselves. A parent may secretly harbor fears that the child may have inherited their sleep problems or worse yet a parent may blame the other parent’s side of the family! Another common scenario may be a parent who has subacute obstructive sleep apnea (OSA). In other words, the parent has symptoms of OSA that have not been recognized nor treated. Now when that person becomes a new parent, the typical household interruptions of a newborn’s sleep may be particularly burdensome. Clearly the parents’ prior sleep history may be very important to help these families.

A clinician must also take a moment to understand the composition of the household. You need to know if there are grandparents, children, and other family members in the home. You need to know where these people sleep and with whom. Did a parent give up a bedroom for a visiting family member, or was somebody displaced to a couch? Have in-laws come for an extended visit to help with the newborn and what happened if and when they left. This is why the symptoms of the patient, in this case the child, must be interpreted in light of how they impact the entire family. A comprehensive approach may require that other family members also be evaluated and treated for sleep disorders.

For new parents the closest opportunity they may have to getting back to their lifestyles before they were parents is when their child is sleeping. Due to this an unnecessarily large amount of pressure may be placed on the family or on a particular parent “to get” the child to sleep. This can create tension in the household. If there is difficulty with a child not sleeping, the usual bedtime routines may be viewed as a chore by the parents. They may begrudgingly take turns to help the sleepless child settle in for the night. It may be worthwhile to gently remind frustrated parents that they do not have to “get” their children to breathe or get hungry. Perhaps the strategies they are using to try to get a child to sleep may be the wrong approach and may even be causing a paradoxical arousal in the child.

Unquestionably, lack of sleep affects mood. The clinician must be prepared to work with parents who may be irritable or angry due to lack of sleep in themselves. They may also feel guilty that their child is not sleeping. Parents may be short tempered or frustrated with each other due to lack of sleep. The frustration or anger can also be directed at the healthcare provider. With adolescents the day may begin with an argument about getting up in the morning and a stressful effort to get to school on time, and the day ends with another argument about bedtime. Parents attempt to correct an adolescent’s behavior may lead to resentment among family members that further exacerbates the sleeplessness. If the parent of the adolescent cannot trust their child to wake up in time, the parent that takes on the responsibility of getting the household started in the morning may develop their own sleep problems.

The clinician working with sleep disorders in children will encounter a wide range of family situations and compositions. Within every family unit, sleep disturbance of the younger members tends to affect every other member of that unit. A common situation, for example, is for a dual income young couple when they first become parents for one of them to at least temporarily give up their employment or income stream. This puts pressure on the parent that continues to bring in an income to retain their employment and perhaps think they should not let their new role as a parent interfere with the work or career. The parent who "gets to stay home" may feel the additional pressure of not only being the primary caregiver to the child but also that the child's sleep does not disrupt the sleep of the parent who "has to go to work" in the morning. When the child sleeps well, the rest of the family may be in harmony. That family will not be making an appointment to talk to you about sleep. However, if the sleepless child is disrupting the sleep of the other family members, there may be resentment between the parent who "gets to stay home" and the parent who "gets to go to work." Sometimes two parents will come in with an infant or young child, and it is not until they are directly asked will you learn that the couple is now separated. The sleep history in one household may be completely different than in the other. Certainly, the presence of environmental allergens must be considered in both homes. Given the dynamic, complex, and nuanced situations that can occur in families, it is not surprising that a clinician can find working with a sleepless child and their families to be very challenging. As the healthcare provider tries to unravel all of this history from the parents, in the limited time allotted for the clinic visit, so often the infant is sleeping peacefully in their arms, or the young sweet child is angelically playing. It is hard to reconcile what is in front of you with the havoc being described.

There is then a whole of other layers of complexity when we consider the sleepless adolescents. Some may consider the parenting of adolescents to be the biggest challenge for parents. Adolescents have a wider range of societal, psychological, and biological factors that can disturb their sleep. As mentioned many households end the day with arguments about going to sleep and start the day with arguments about getting up in time for school. The adverse consequences of sleeplessness in an adolescent may be far worse than in a younger child when you consider, among other things, the greater academic demands, the potential presence of suicidal ideations, and the increased risks for automobile accidents.

When evaluating and treating a sleepless child, it is important to understand that sleep is a biological process which has a learned component. It is analogous to eating. The need for food is biological, but what you eat is learned over time and may change. A child who has had negative experiences sleeping may become an adult with lifelong sleep problems, who then passes on these problems to their own future children. Yet the reality is that the majority of sleepless children are readily treatable often with a good prognosis. This chapter will describe therapeutic approaches to helping infants, young children, and adolescent sleep better with an emphasis on behavioral approaches. In addition, medication options will also be discussed which can, depending on the clinical situation, sometimes be a part of the therapeutic plan.

Socioeconomic Impact of Sleep Disorders in Children

Improving the sleep of children can improve the maternal well-being and lower the cost of healthcare utilization. This was demonstrated in an Australian study that offered behavioral interventions to infants whose mothers complain of poor sleep at 7 months of age. Follow-up at 10 and 12 months showed improved maternal mood, overall health, and lower medical costs [1].

There is limited data on prospective healthcare utilization by children affected by sleep disorders. In 2013 [2], an Australian cross-sectional study that sampled "birth" cohort at ages 0–1 year and 2–3 years old and "preschool" cohort at ages 4–5 and 6–7 reported those that exhibited sleep problems utilized more healthcare compared to their peers. Federal Medicare expenditure captured 98% of all children registered in Australia. The Longitudinal Study of Australian Children (LSAC) evaluated 5107 children at ages 0–1 years in 2004 and 4606 of these children at ages 2 and 3 in 2006. The older group looked at 4983 children ages 4 and 5 and later at ages 6–7. These children were compared to matched controls within randomly selected postal codes. Among all the subjects, 92% had complete sleep and Medicare data. Of children with reported sleep problems, the average additional annual healthcare cost at age 5 was $141 and for age 7 was $43 (in 2012 Australian dollars). Adjusting for confounders, the increase in healthcare costs was $98 at age 5 and $18 at age 7. The estimated cost to the Australian government was $27.5 million (95% CI $9.2 to $46.8 million). This same group also studied the healthcare costs of children up to age 7 with "special healthcare needs" and estimated the additional costs at $161.8 million [3]. It would not be surprising that children with both chronic sleep disorders and additional special healthcare needs would have higher healthcare utilization and accompanying costs in any society [4].

An estimate of 20–30% of infants, toddlers, and preschoolers may present with behavioral challenges in going to sleep and repeated awakenings according to a 2006 review [5]. A report in 2014 [4] by L. Meltzer et al. showed only 5% of representative samples of pediatric and adolescent patients that reported either sleep problems or diagnosed with a sleep disorder actually received sleep-related treatment recommendation. Only 8% of children diagnosed with sleep disorders and 2% identified with sleep problems received "any type of treatment recommendation." Of 750 children who had well-child visits in urban and suburban primary care settings in Philadelphia, 520 youth (69%) Year 1, 490 (65%) Year 2, and 451 (60%) Year 3 had documented follow-ups from 2007 through 2010. Of these, 150 were randomly selected, and the average ages were 6.21 years. More sick visits and calls were incurred among children who had sleep disorders than those without. Up to 1/3 of children showed persistence of sleep problems "across time." The families with lower income tended not to have follow-up visits. These results point to how difficult it is to accurately estimate the socioeconomic impact to society of sleep disorders in children.

One of the challenges of confronting the socioeconomic impact of sleep disorders in children is the sense that not only is it an immense problem that is hard to define but that the treatment is expensive and labor-intensive. However when it

comes to adolescent's sleep, technology may offer an effective and less costly options by allowing cognitive behavioral therapy to be available online [6]. In this study 62 teenagers in Amsterdam with insomnia were randomized to either face-to-face CBT sessions or Internet-based CBT sessions. Both groups improved when re-evaluated after 1 year, but the Internet group had lower costs [6]. Over time as the cost of manpower increases and cost to access the Internet decreases, the advantages of Internet-based CBT should be even greater. This study using online CBT has concluded it can be effective, affordable, and readily available. Cognitive behavioral therapy is currently considered the first treatment for chronic insomnia [7].

Sleepless Infants and Young Children

How do we define a sleepless infant or young child? Since they cannot make an appointment, the initial concern about sleeplessness will be raised by the primary parent/caretaker. Parents of these young children may often ask how many hours should my child sleep. Therefore an initial approach to evaluating this question or concern is by determining how many hours the child is sleeping. This is typically based on history provided. More objective measures of the amount of sleep such as actigraphy are rarely available at the initial evaluation. The American Academy has provided a consensus statement on the recommended amount of sleep for children [8–10]. They recommended infants 4 months to 12 months old should sleep 12 to 16 hours per 24 hours (including naps). Children 1 to 2 years of age should sleep 11 to 14 hours including naps. Children 3 to 5 years of age should sleep 10 to 13 hours per 24 hours. Children 6 to 12 years of age they concluded should sleep 9 to 12 hours per 24 hours on a regular basis to promote optimal health. The National Sleep Foundation has also issued recommendation for the amount of sleep in children [11]. They recommended similar amounts but broke down the age brackets a little differently. The sleep duration recommended for newborns is between 14 and 17 hours, infants between 12 and 15 hours, toddlers between 11 and 14 hours, preschoolers between 10 and 13 hours, and school-aged children between 9 and 11 hours. These recommendations are based on expert consensus opinions and can be helpful when discussing with parents how much sleep time they should expect or allot for their children. An exceptional study by Iglowstein and colleagues that carried out a longitudinal study for over 16 years to measure how sleep amounts changed in a cohort [12].

The complaint of sleeplessness for infants and young children should be distinguished from the diagnosis of insomnia. For example, a child with leg discomfort due to restless leg syndrome may be sleepless but would be more appropriately diagnosed with a sleep-related movement disorder rather than with insomnia. However the child's complaints may induce insomnia in the parents. Another example is if a child has trouble sleeping due to an acute illness such as an ear infection, the symptom of insomnia could be transiently present. Insomnia in general refers to difficulty falling asleep and/or staying asleep to the point that it bothers a person the next day. Insomnia is a symptom that can become a diagnosis. It may be comorbid

with other conditions. When this occurs, the term "secondary insomnia" is discouraged since it is misleading to think that resolving one medical problem will automatically correct the insomnia symptoms. Insomnia among children is reported by parents when there is bedtime resistance, frequent awakenings, or difficulty sleeping without a parent's intervention or the child will not sleep alone and interrupts the parent's sleep. Persistent insomnia over time can evolve into an insomnia disorder. The third edition of the International Classification of Sleep Disorders (ICSD-3) simplified and consolidated the previously described insomnia subtypes in children into the same diagnosis used in adults, chronic insomnia disorder [13]. This disorder requires the presence of symptoms to occur at least three times per week and be present for at least 3 months. In the ICSD-3 the daytime symptoms of chronic insomnia disorder in children includes fatigue; attention or concentration impairment; impaired social, family, or academic performance; irritability; daytime sleepiness; and behavioral problems such as hyperactivity, impulsivity, and aggression. The diagnosis requires that the symptoms be present despite adequate time and circumstance to sleep.

As mentioned above a fundamental concept in understanding sleeplessness and insomnia in children is that the *need* for sleep is a biological drive, but sleep is also a *learned* behavior. In children this means that sleep-onset associations or limit-setting behavior may characterize the insomnia behavior. Sleep-onset associations are based on the realizations that all of us will have brief arousals or awakenings during the night. Usually we are able to continue sleeping without requiring assistance. In infants and small children, they may have learned associations with falling asleep such as feeding or being rocked. When they have their normal spontaneous arousals, they may be unable to return to sleep unless the associated learned circumstances are recreated [14]. The clinician can help the family identify what associations with sleep the infant or child has learned and then help teach them new associations which are less disruptive to the family. Of course in the situation of infants and very young children, they may not have any incentive to learn new sleep associations and may strongly protest. From the infant's perspective, they may very well enjoy being rocked to sleep and fed on demand by the person that loves them the most in the world. Parents may have mixed feelings about trying to modify the sleep situation. For example, parents may tell you they want to change an infant's behavior but do not want the infant to cry.

Insomnia in children is not homogenous, and it is important to briefly review the typical age-related presentations of insomnia. In infants insomnia may be related to nocturnal feeding, sleep-onset association type, or behavioral insomnia of childhood. Other potential occult reasons for disrupted sleep include allergies, gastroesophageal reflux, and sleep-disordered breathing. Infants will learn associations for sleep. The associations children make with sleep, such as the presence of a parent with sleep onset, may help them to sleep throughout the night. If these associations are not there, the infant may have difficulty sleeping.

With toddlers and preschool children, nighttime fears may lead to sleeplessness. Children in this age group may associate a dark environment with being left alone, since the only time they are left alone for extended periods at time is when they are in the dark. Children expressing fear of the dark may be expressing a fear of being

left alone. Sleep-deprived parents may find leaving a light source on at night may in the short term improve a child's sleep. However it also risks reinforcing the feeling that there is something to fear in the dark leading to more sleeping difficulties in the long run. Parents or the child may become convinced that the child cannot sleep unless a light is left on. Other attempts to reduce fears with special routines or items may also have similar results. Parents may describe that various rituals that are needed to help a child fall asleep seem to work at first only to fail later or need another item or ritual added. The root of the nocturnal fear needs to be addressed. It may be helpful to point out to the family that there is a difference between feeling safe and being safe. If the child is expected to sleep in a separate room from the parents, the child needs to learn to feel safe in a dark environment away from the parents. Creative solutions that fit the family can be discussed with the family to help the child to learn to trust being alone in the dark for sleeping. For example, parents can model how they like to sleep in the dark. With an older child explaining the paradox that we are safer sleeping in the dark than exposed in the light may be useful.

Behavioral insomnia can be differentiated from insomnia due to a physical problem by observing how the child sleeps with and without the parent in the same space. If the child sleeps better with the parent, then more likely the child is experiencing behavioral insomnia. If the infant sleeps poorly even with the parent then a physical problem should be more closely considered.

Restless leg syndrome in a very young child is an example of a physical condition that may manifest in sleeplessness. The diagnosis of restless leg syndrome is entirely based on the history of unpleasant hard-to-describe feeling in the legs often accompanied by an urge to move the legs. Movement of the legs can provide temporary relief. The symptoms occur predominately at night or while resting [13]. Since the diagnosis is made based on the history provided if a child cannot express themselves, the diagnosis will be difficult to make [15]. With restless leg syndrome there may be a history of sleep difficulty due to "growing pains." Restless leg syndrome has a strong familial pattern [16]. For very young children who cannot adequately express themselves, the diagnosis may be suspected based on obtaining a family history. Restless legs may have a variable expression but do tend to flare up during pregnancy, which the birth mother may recall when asked.

There are several self-help books targeted for new parents that putatively offer solutions to help infants and young children sleep. Most of these books have conflicting information since each new book must contradict the previously published books to justify its own publication. It is not unusual for parents of a sleepless child to have been overwhelmed by conflicting information and advice.

Practice parameters for the behavioral treatment of bedtime problems and night awakenings in infants and young children have been published [17]. Many of these recommended behavioral techniques involve some form of **extinction** where parents allow a child to cry. This may be in the form of unmodified extinction which involves parents putting the child to bed at a designated bedtime and then ignoring the child until morning, although parents continue to monitor for issues such as safety and illness. The goal is to reduce undesired behaviors (e.g., crying, screaming) by eliminating parental attention as a re-enforcer. A variation is graduated extinction which

involves parents ignoring bedtime crying and tantrums extinction for pre-determined periods before briefly checking on the child. A progressive (graduated) checking schedule or fixed checking schedule (e.g., every 5 minutes) may be used. Like unmodified extinction, the goal is to enable a child to develop "self-soothing" skills and be able to fall asleep independently without undesirable sleep associations [17]. Many parents have difficulties implementing and maintaining these procedures, leading to attrition, non-compliance, and treatment avoidance [18]. Another behavioral technique has the somewhat cumbersome name of positive routines/faded bedtime with response cost. Positive routines "involve parents developing a set bedtime routine characterized by enjoyable and quiet activities to establish a behavioral chain leading up to bedtime sleep onset. Faded bedtime involves temporarily delaying the bedtime to more closely coincide with the child's natural sleep-onset time and then fading it earlier as the child gains success falling asleep quickly. Response cost involves taking the child out of bed for prescribed brief periods if the child does not fall asleep. These strategies rely on stimulus control as the primary agent of behavior change and target reduced affective and physiological arousal at bedtime" [17]. This approach is more in line with the more recent recommendations for the treatment of adults with chronic insomnia with cognitive behavioral therapy [7, 19].

When discussing behavioral technique options for sleepless infants and young children, parents may ask which is the best approach or are there any long-term adverse outcomes from ignoring a child's crying. There is evidence that more than one approach can be effective without an adverse effect on the child. A randomized trial in Australia with total of 43 infants using either graduated extinction or bedtime fading was compared to a control group that only received sleep educational information. The study included both subjective (diaries) and objective (actigraphy) sleep measurements. In addition infant stress was measured via morning and afternoon salivary cortisol sampling and mothers' self-reported mood and stress. Twelve months after the interventions, there were large decreases in sleep latency, number of awakenings, and wake after sleep onset for the graduated extinction group. The bedtime fading group also had improved sleep latency. Salivary cortisol decreased compared with controls as did the mothers' stress. The authors concluded that both graduated extinction and bedtime fading provide significant sleep benefits compared to the control group without "adverse stress responses or long-term effects on parent-child attachment or child emotions and behavior" [20].

The clinician must keep in mind that they should not be imposing their cultural beliefs on the family. Before attempting to apply these techniques, all members of the family must be in agreement that there is a mutually agreed goal to have the child sleep through the night without feeding while at the same time not discouraging nursing when the child is awake. Another common question is how young a child can these techniques be applied. An infant needs to be old enough to not require nighttime feedings. For a healthy child, this is usually between 3 and 6 months of age. You can ask a parent what is the longest single stretch of time the child was able to go between feedings and use that as a guide. Crichton and Symon reviewed the data on behavioral sleep techniques for children younger than 6 months. They reviewed 11 studies and concluded behavioral techniques were effective in improving infant sleep

and long-term follow-up studies "have failed to find any negative effects on the child, either from a psychological or physical perspective" [21].

In situation when behavioral treatments have not been effective or in which special circumstances arise, the use of medication to help an infant sleep may be carefully considered. Medication options for sleep are discussed in more detail below. For otherwise healthy infants, one of the first medications they are exposed to ever is over-the-counter acetaminophen. They may receive acetaminophen for fever associated with immunizations or viral illness. During these times the infant may appear to sleep better than usual to some parents. This may explain why some parents may subsequently give an infant acetaminophen for sleeping difficulties. The ready availability of alcohol allows it to be given by some parents to their infants in a putative attempt to help them sleep. Some infants may have also been given antihistamines, which are further discussed below. Since acetaminophen, alcohol, and antihistamines are all available over-the-counter in liquid form, they are readily available for sedation of an infant. Parents may not volunteer that they have already tried these substances before seeing a clinician. The clinicians should specifically ask about this when taking a history. Parents and clinicians must understand that sedation is not the same as normal sleep.

In older toddlers and young school-age children, problems with sleep may be related to bedtime refusal or limit-setting problems. Limit setting is characterized by stalling or negotiating behavior due to the parent not enforcing consistent rules at bedtime. These children may also have a history of excessive daytime tantrums. These children will more often have difficulty falling asleep as opposed to trouble staying asleep. This pattern of behavior needs to be distinguished from children that have bedtimes that are too early. These bedtimes may have been chosen for the parents' convenience when a child is not yet physiologically sleepy. As will be discussed below in adolescents, there are circadian rhythm principals that need to be considered. Just like adults, children will have times of heighten alertness in the evening. This is usually a couple of hours before their usual falling asleep time. Trying to force a child to sleep during this window of time is an unnecessary uphill battle. The faded response technique described above relies, in part, on a delaying bedtime to a more appropriate when the homeostatic drive for sleep and circadian time for sleep are more aligned.

All children may benefit from a predictable soothing bedtime routine and sleep environment, especially if they are sleeping alone. The bedtime routine must provide a feeling serenity. We want children to learn that when they are in bed at night, they are safe, comfortable, and loved.

Sleepless Adolescents

The reader may have wondered why this chapter title uses the term "sleepless" instead of insomnia. Sleeplessness in adolescents is characterized by difficulty falling asleep, rather than staying asleep. This form of sleeplessness can be characterized as a "sleep-onset insomnia," but it is not classified in the ICSD-3 as an insomnia

diagnosis. Instead it is classified as a circadian rhythm sleep-wake disorder, namely, delayed sleep phase syndrome (DSPS) [13]. DSPS is a circadian rhythm sleep disorder characterized by chronic sleep-onset insomnia, without sleep maintenance insomnia, and an inability to rise at a time in the morning that is appropriate given the individual's commitments. There is a delay in the phase of the major sleep episode in relation to the desired or required sleep and wake-up times. This results in difficulty falling asleep and difficulty getting up in time in the morning when they have to go to school. When the adolescent can set their own schedule, for example, while on vacation, they sleep well and do not have difficulty falling asleep or getting up. This is a common way for sleeplessness to present during adolescence.

Perhaps the first sign of a sleep disorder in an adolescent is having a widely different wake-up time of at least 2 hours between schooldays and weekends. It is unusual for young children to sleep in on weekends because they are not systematically sleep deprived during the school week, unlike adolescents [22]. Any clinician working with adolescents must strongly consider the possibility of sleep deprivation being present to some degree [23]. The onset of puberty marks a biological tendency for adolescents to fall asleep later at night [24–26]. This is why starting school later in the morning is strongly advocated for adolescents [27–30]. The clinician must obtain a history of sleep schedules on weekends compared to weekends and also what time school starts as well as how early the adolescent needs to wake up to make it to school on time. Adolescence susceptible to DSPS may have more difficulty adjusting to an earlier sleep time than others. Once the DSPS patient is able to fall asleep, he sleeps soundly for a normal duration. When not required to maintain a strict sleep schedule (e.g., on weekends or during vacations and holiday periods), patients will awaken spontaneously, albeit late in the morning or early in the afternoon. The ability to experience refreshing sleep is a key factor in a pure case of DSPS. If a teenager does not report waking refreshed after sleeping for several days on a stable schedule of his own choosing (sleeping late on a weekend may not provide sufficient time to establish whether or not sleep is truly refreshing), a comorbid condition should be suspected. It is worthwhile knowing that DSPS was originally described in a group of young adults who had previously been thought to have an atypical depression that did not respond to conventional depression treatments [31].

DSPS is a relatively easy diagnosis to make once there is a clinical suspicion. The prevalence is estimated to be about 7–16% of among adolescents and young adults [13]. However successful treatment can be very challenging since, like other circadian disorders, it requires the motivation of the adolescent to make the necessary lifestyle changes to resynchronize their sleep-wake schedule with societal expectations. If the adolescent acknowledges that there is a problem and wants help, then an initial step is to help them understand the basics of how their circadian system works within them.

Behavioral adjustments can be effective in treating DSPS [6, 32, 33]. DSPS can be conceptualized as resulting from a clock for which the time can only be readily adjusted in one direction, as it is intrinsically easier for patients to fall asleep later than usual, rather than earlier. Chronotherapy was the first successful treatment for

DSPS based on resetting the adolescent's sleep using a series of consecutive time delays of the bedtime and wake time over several days to get to the desired schedule. To maintain the new schedule, the adolescent is encouraged to keep the new bedtime and wake time daily including weekends. In practice this treatment is cumbersome and impractical since the adolescent would temporally have to stay up all night and sleep in the day as their schedule is swung around the clock. Instead it may be preferable to start by determining what is the earliest time the adolescent has woken up recently, fix that time, and move it back to the desired time for school and social commitment. Napping is discouraged to increase the homeostatic drive to sleep at night. Bright light in the morning, phototherapy, is used as an adjunctive treatment to entrain the fixed wake-up time. Phototherapy is based on the principle that bright light in the morning can phase-advance the circadian clock to counter the sleep-wake phase delay of the adolescent [34]. Phototherapy is discouraged in people with retinal disease or a history of bipolar disorder [25, 26].

Since DSPS is a circadian disorder, the use of melatonin as a circadian modulator is of used as a treatment option [33, 35]. Melatonin is a hormone secreted by the pineal gland that influences the timing of our biological rhythms. Melatonin is perceived to be safe by many people because it is available over the counter in the USA [33, 35]. This has led to it being used in a wide variety of clinical situations characterized by poor sleep. In general melatonin may help shorten the time to fall asleep but does not typically increase the total sleep time [36]. It will be discussed further below.

Hypnotics

Sleepless behavior in a child or adolescent may disrupt the pattern of sleep of the household. Often behavioral therapy is sufficient treatment for this insomnia pattern. However in the situation of an extremely anxious or of a special need, child adjunctive pharmacotherapy may be requested by the parents. Before making any pharmacological recommendations, the clinician should keep in mind that this is an age group with possible undiagnosed allergies, gastroesophageal reflux, obstructive sleep apnea, or restless leg syndrome. The medications physicians are likely to recommend in this group are also the antihistamines since they are available in liquid form. Other medications used in this age group are benzodiazepines such as clonazepam which is available in a sublingual form. Melatonin is also often tried by parents and clinicians in this age group [37]. Some clinicians, in particular child psychiatrists, will recommend clonidine, an alpha2-receptor agonist, in this population. The use of a wide range of sedating medications is in clinical use in these children including trazadone, atypical antipsychotics, anticonvulsants, and short-acting hypnotics [38]. If the insomnia persists as the child grows older, a litany of agents may have been unsuccessfully tried.

It is a commonly described phenomenon of children receiving sedating medication or hypnotic and becoming agitated instead of sleepy. This was described as a "paradoxical reaction," and typically no further explanation would be offered to the

bewildered parents other than this happens sometimes. However patients and their families deserve a better explanation. Why would a sedating medication have such a profoundly opposite effect? In retrospect, these paradoxical reactions may have been due to inadequate dosing, not taking into account the circadian principles of sleep tendencies or the child's state of mind at the time. In the absence of clear pharmacological guidelines, the natural inclination is to give the lowest possible dose of a medication to a child. However when treating a child, especially one with a neurological or psychiatric condition, if the dose of medication is underestimated or administered at a time of heighten circadian alertness, the medication may disinhibit the child or create a dissociative state. The child may not have understood they were expected to go to sleep and may have had heightened arousal due to the novel and or perceived scary environment. The emergence of hypnagogic hallucinations may frighten the child or be misinterpreted as a delirium or psychotic reaction. Prior food intake may also interfere with absorption of the medication, or the child's usual medications may have induced hepatic enzymes or have other interactions further complicating the hypnotic administration consideration [39].

Owens et al. published a national survey for pharmacotherapy for insomnia among child psychiatrists in 2010 [38]. The ages of children/adolescents were reported as 6–10 years, 10–20 years, and >20 years. A surprising wide range of medications were being prescribed and recommended with little evidence-based data to support it. The authors concluded that insomnia is a significant clinical problem in children treated by child psychiatrists for a variety of behavioral, neurodevelopmental, and psychiatric conditions. In addition there was a worrisome highly variable clinical approach to insomnia children.

Melatonin is frequently used for delayed sleep phase syndrome and jet lag as it may have a phase-setting effect on the body. In adults taking melatonin, small amounts prior to bedtime are thought to be effective in raising the plasma melatonin to normal levels. The doses which may be effective in children are unclear [35]. An analysis of over-the-counter melatonin in Canada raised strong concerns about the quality of the product [40]. Erland and colleagues analyzed melatonin by ultraperformance liquid chromatography in 30 commercial supplements. Melatonin content was found to range from −83% to +478% of the labelled content including within the same brand. Serotonin was found in 26% of the samples. Melatonin content did not meet the label within a 10% margin of the label claim in more than 71% of supplements. An accompanying commentary to this article called for greater regulation of the sale of melatonin [41]. This lack of regulation may cause the quality of over-the-counter melatonin to be highly variable.

Melatonin has been used in children with sleeplessness due to circadian factors such as sleep phase delay disorder and blindness and patients with midline brain defects such as agenesis of corpus callosum as this may affect the pineal gland. Children with poor sleep associated with neurological syndromes have also had some positive outcomes [37]. A randomized trial of melatonin was compared to bright light treatment, and a control was done with 84 children (average age was 10 years old) [42]. The authors found that both melatonin and bright light treatment were able to shorten sleep latency but the effect was stronger with melatonin.

In clinical practice both of these treatment options can be combined depending on the clinical situation.

Ramelteon, a melatonin receptor agonist, has been approved for use in patients 18 years and older with sleep-onset insomnia [43–45]. It has been reported to help the sleep of people with autistic spectrum disorder [44, 46]. It may be considered in adolescents with sleep phase delay syndrome. However no clinical trials are available for patients younger than 18 years old. There was at least one report of it being used for the treatment of night terrors and sleepwalking in children [47].

Tasimelteon is a melatonin receptor agonist which was released by the FDA for the treatment of non-24-hour sleep-wake disorder in 2014. It has an affinity for human melatonin receptors MT1 and MT2, with a higher affinity for the latter. The clinical trials were done in blind adults with a circadian disorder [48, 49]. Safety and efficacy have not been established in pediatric patients. There is a hypothetical possibility that this new medication may be useful to help entrain the sleep of children with significant circadian disruption to a more predictable schedule. However, to date there are no pediatric studies available.

Benzodiazepines and benzodiazepine receptor agonist can be considered as therapeutic options to improve sleep [50]. The benzodiazepine, clonazepam, is available in low-dose sublingual wafers that allow for easier administration. Benzodiazepines are hypnotics that act as a GABA receptor agonist. The most commonly used benzodiazepine used in children for sleep is clonazepam. Clonazepam has been used for arousal parasomnias such as sleepwalking and sleep terrors in children [51]. Clonazepam may allow the child to sleep throughout the night and is thought to decrease the arousal threshold. This drug may be beneficial if this behavior is frequent and disturbing to the patient or family. A dose of clonazepam at 0.25–0.5 mg may be used. Benzodiazepines may lead to muscle relaxation, and therefore caution is advised in children with obstructive sleep apnea as it may exacerbate the condition.

Selective benzodiazepine receptor agonists including zolpidem, eszopiclone, and zaleplon are thought to offer some advantages compared to nonselective benzodiazepines. These selective benzodiazepine receptor agonists at low dosages are thought to preserve the overall sleep architecture and are thought to have less insomnia rebound effects after discontinuation when compared to nonselective benzodiazepines. These medications only have FDA approval for use in patients older than 18 years old, and therefore the use of these medications in children is considered "off-label." There are reports of zolpidem abuse among adolescents [52, 53].

Sleep and Allergies

Sleep disorders in general and obstructive sleep apnea in particular are commonly encountered conditions in allergy practice. Obstructive sleep apnea along with the entire spectrum of sleep-disordered breathing (SDB) may present with sleeplessness. The clinician suspicion for SDB in a child should not limit solely to those that snore loudly or appear sleep and tired. Any nasopharyngeal obstruction from

rhinitis, nasal polyposis, or adenotonsillar hypertrophy may contribute to audible breathing and obstructive breathing events. An allergist does not need to limit their management of continuous positive airway pressure intolerance. In 2015, an Internet-based survey of active American Academy of Allergy, Asthma & Immunology members was performed to determine perceptions and practice regarding SDB. Only 7% of active members returned the survey (339 of 4881). Most of the respondents reported that SDB was a problem for at least a "substantial minority" (10–30%) of their adult patients and believed that medical therapy for upper airway inflammatory conditions could potentially help ameliorate sleep-related complaints. The authors supported "the connection between high-grade nasal congestion/adenotonsillar hypertrophy and obstructive sleep apnea, and at least in the case of pediatric patients, supported the use of anti-inflammatory medication in the initial management of obstructive sleep apnea of mild-to-moderate severity." They called for allergists to be proactive role in the diagnosis and management of sleep-disordered breathing [54].

Children with atopic dermatitis can experience significant sleep disruption since it worsens at night. Epidemiologic findings of atopic dermatitis impaired growth. A sleep assessment is considered a crucial component of clinical management. Treatment options that address the sleep disturbance are future directions for research [55].

Although conditions with nasal obstruction or nocturnal eczema would be expected to disrupt sleep, sleep disorders are often underreported to physicians by patients and with allergies their families. A French prospective study of children and adults was done to characterize the sleep disorders associated with respiratory allergy to house dust mites at the time of initiation of immunotherapy. The study included 843 children older than age 5 suffering from dust mite allergy. The majority of the children (66%) reported that their sleep disorders prompted their medical consult. The most commonly observed sleep complaints for the children were snoring in 41%, poor-quality sleep (37%), and nocturnal awakening (28%). Difficulties falling asleep were reported by 25% of children. Children suffering from severe persistent allergic rhinitis experienced sleep complaints significantly more often than those with only intermittent or mildly persistent rhinitis. This study confirms that a sleep history should be part of the evaluation of allergies. This is particularly true when severe allergic rhinitis is present [56]. Clinical practice guidelines specifically recommend that clinicians should assess patients including children with a clinical diagnosis of allergic rhinitis for comorbid SDB [57].

SDB, in children with comorbid asthma, may exacerbate asthma control. A study of 408 children with an average age of 8 years found that sleep-disordered breathing and tonsillar hypertrophy were independent risk factors for poor control in these asthmatic children. The authors concluded that "tonsillar hypertrophy may have a role in the association between" sleep-disordered breathing and not-well-controlled asthma in childhood [58]. A systematic review to describe the relationship between asthma and SDB in children found children with asthma were more likely to develop habitual snoring and obstructive sleep apnea. Children with SDB were more likely to develop asthma. Asthma was associated with more severe OSA, and the presence

of SDB was associated with severe asthma. The authors concluded there was a bidirectional relationship between asthma and SDB and adenotonsillectomy appears to improve both conditions [59].

Some clinical populations may require closer attention. Zandieh and colleagues reported a group of 9565 urban adolescents. Compared to those without probable asthma, adolescents with probable asthma had 2.6 greater odds of reporting SDB symptoms which increased with severity. The authors concluded that among urban adolescents with self-reported SDB symptoms, there was an association with probable asthma and increased asthma severity. This is important since SDB treatment may improve asthma control [60].

The presence of comorbid asthma may be an important consideration when considering the treatment approach to SDB. A study by Mukhatiyar and colleagues found that the comorbid asthma may help predict the efficacy of the adenotonsillectomy type. They compared the outcomes of intracapsular versus extracapsular adenotonsillectomy and found that the SDB was more likely to be refractory to treatment with intracapsular adenotonsillectomy compared with the extracapsular type [61].

Conclusions

There are many reasons a child may be considered to be sleepless. Fortunately, the vast majority of these children can receive effective treatment after a careful initial evaluation is performed. Behavioral treatments should be the principal therapeutic approach. Medications can be carefully considered as adjunctive treatment options in selected clinical situations.

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Evaluation and Management of Movement Disorders in Children

10

Luis E. Ortiz and Christopher Cielo

Sleep-related movement disorders are a highly variable group of conditions that are generally benign but need to be able to be distinguished from more serious conditions.

General Assessment of Sleep-Related Movement Disorders in Children

Sleep-related movement disorders (SRMD) that can be found in children are reviewed here (Table 10.1). In general, the history obtained from the parents, and sometimes the patient, is diagnostic for SRMD. In addition to a thorough description, a video of the movements can also be very helpful. It is important to determine if these movements occur outside of sleep or the period of sleep onset as SRMD are typically restricted to this time. Complex movements or goal-directed actions that may present during sleep but can also present during wake include Tourette syndrome, dystonia, epilepsy, habitual self-soothing movements, or other mimickers of SRMD (Table 10.2).

In cases where the diagnosis is not clear from history, the evaluation may benefit from polysomnography. Polysomnography is a standardized continuous video and multichannel recording of physiological parameters during sleep. These recordings usually occur overnight and in children are typically performed in an attended

L. E. Ortiz
Sleep Center, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

C. Cielo (✉)
Sleep Center, Department of Pulmonary Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA
e-mail: cieloc@email.chop.edu

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Table 10.1 Features of sleep-related movement disorders

	Brief description
Restless legs syndrome	Leg discomfort at night and rest, causing irresistible urge to move legs. Results in disrupted sleep or difficulty initiating sleep. Correlation with ADHD
Periodic limb movement disorder	Repetitive, highly stereotyped limb movements. Results in frequent arousals leading to daytime symptoms. May precede RLS in children
Sleep-related leg cramps	Leg cramping at night that can occur prior to or after sleep onset. Not thought to be physiologically different from leg cramps in other situations but can be associated with medical conditions such as diabetes mellitus, dystonias, and metabolic derangements (hypokalemia, hypomagnesemia)
Sleep-related bruxism	Repetitive jaw clenching or grinding of teeth resulting in tooth wear or jaw pain/discomfort. Primary bruxism can be seen in normal, healthy children but can be associated with stress or anxiety. Secondary bruxism is often observed in children with cerebral palsy or mental retardation. High rate of OSA comorbidity
Sleep-related rhythmic movement disorder	Repetitive, stereotyped, and rhythmic (~2 movements/sec) motor behaviors such as body rocking and headbanging. Typically occurs at sleep onset but can occur during quiet activities. Common in infants and tapers off in early childhood. Can persist through adulthood in developmentally normal individuals
Benign sleep myoclonus of infancy	Repetitive myoclonic jerks only during sleep in neurologically normal neonates and infants. Typically presents at age 1 month. Can occur with the whole body or isolated to the limbs, trunk, or face. Resolves between ages 3 and 6 months

Table 10.2 Imitators of sleep-related movement disorders

	Brief description
Autoerotic behaviors	May involve body rocking or rhythmic movements but primary focus is genital stimulation
Tourette's disorder	Tics that occur during wake, may be present prior to sleep onset
Seizure	Stereotyped movements that may occur during wake and sleep
Self-soothing repetitive motion	May include thumb sucking
REM behavior disorder, sleep walking, confusional/partial arousals, and other parasomnias	Occur during sleep. Complex goal-oriented actions. Secondary to incomplete transition to sleep states or slow transition to wake

sleep laboratory. Polysomnography includes a video recording of the patient, a limited electroencephalogram used to stage sleep and score arousals, measures of airflow and respiratory effort, pulse oximetry to determine hypoxemia, and electromyography to detect leg and chin movements. Polysomnography is necessary to make the diagnosis of some conditions, such as periodic limb movement disorder. The limited electroencephalogram can be used to screen for seizure activity as well. In these cases, the video recording can be helpful in visualizing the

movements and correlating them with physiologic measures recorded during polysomnography and technician notes during the study.

Specific Sleep-Related Movement Disorders

Restless Leg Syndrome

Restless legs syndrome (RLS) is an almost irresistible urge to move the limbs, typically due to uncomfortable sensations deep in the limbs at night prior to sleep onset. This leads to delayed sleep onset and difficulty resuming sleep following arousals [1]. Per the ICSD, (1) symptoms must begin or worsen with rest or inactivity; (2) the uncomfortable sensations must be partially or completely relieved with movement; and (3) symptoms must have a circadian timing, with worsening symptoms at night. These symptoms cannot be explainable by other medical or behavioral issues (cramps, positional discomfort, habitual foot tapping). Finally, these symptoms must cause disruption of the health or daily functioning of the patient [1]. In children, the description of the symptoms should be in their own words.

RLS is not as rare as previously thought, with 5–10% of European and North American adults expressing RLS symptoms. There is a higher prevalence in women and populations of European descendent. The mean age onset is during the third or fourth decade of life, with incidence increasing with age [2–6]. However, one-third of adult patients in two survey studies report symptom onset during childhood [5, 7, 8]. The pediatric prevalence is estimated to be 2–4% in the US and UK. Unlike adults, there does not appear to be a gender difference in the prevalence of symptoms in children. In children, RLS is often comorbid with ADHD and "growing pains" [5, 9].

The pathophysiology of RLS is not fully understood. However, it is felt that under normal sleep conditions, spinal flexor reflexes and sensory activity of the limbs are suppressed through dopamine signaling [10–12]. This is demonstrated by improvement of symptoms with dopamine agonists, worsening of symptoms with dopamine antagonists, and dopamine receptor knockout animal models showing symptoms similar to RLS [12]. Iron metabolism has also been identified as a key factor in RLS pathology; patients with relative iron deficiency (ferritin <50 μg/L) have improvement of symptoms following repletion [13]. Low iron stores in the brains of patients with RLS have also been demonstrated through pathologic samples, MRI imaging of the basal ganglia, and cerebrospinal fluid measurements [12, 14]. Iron is a cofactor for dopamine production, but low iron has also been found to be associated with dopamine receptor downregulation and aberrant release of dopamine [11, 15–17]. Patients with RLS may also have changes in iron transport proteins, having increased ferroportin proteins which transport iron out of cells which would make cells sensitive to iron deficiency [18]. However, not all patients with RLS are iron deficient or respond to iron repletion, suggesting additional disease pathways [13].

There is a strong familial pattern to early-onset RLS. Twin studies have shown high concordance rates, and having a first-degree relative with RLS increases the risk for developing RLS two- to sixfold [9]. Despite studies showing an almost autosomal dominant pattern of inheritance with a pattern of genetic anticipation, no single gene mutation has been identified with early-onset RLS. Genome-wide association studies have identified several single nucleotide polymorphisms associated with RLS (including MEIS1, MAP 2K5/LBXCOR, and PTPRD). The functions of these genes are mainly related to embryonic neuronal development; however, it is unclear how gene function (or dysfunction) leads to RLS pathology [10, 11, 19].

While kicking before sleep may be a presentation that parents report (especially if bed sharing), complaints of difficulty falling asleep or refusal to go to bed is also commonly reported in children with RLS. It is important to obtain a thorough history, including screening for symptoms that parents may not immediately associate with RLS. This includes the presence of growing pains, the patient's need for leg massaging to help him/her relax when going to sleep, or the presence of ADHD or ADHD-like symptoms (difficulty focusing in school, fidgeting). If limb movements are noticed by the parents, the timing, frequency, severity, and modulating factors of these movements should be assessed. Family history should also be obtained from the parents. Mothers should also be asked if they had RLS-like symptoms during pregnancy as pregnancy can induce RLS during that time period.

When taking an RLS history, one must be mindful of not asking leading questions as the ability of the child to describe the symptoms in his or her own words is an important part of the diagnosis. The international restless legs syndrome study group has developed diagnostic criteria for adults, but in 2003, the NIH released consensus criteria for the diagnosis of RLS in children. These criteria modify the adult criteria to account for differences in how children may experience RLS and their ability to express their symptoms by having the patient describe their limb sensations or urge to move in their own words [20]. The discomfort of a patient with RLS can be difficult to describe, even for adolescents. They may struggle to find the right words to describe their symptoms and often use emotional language ("I've got energy legs," "My legs are tugging") or attempt to connect them to other experiences ("It's like pain, but not pain" or "It's like when your arm falls asleep, but different"). Younger children may not have the language skills or life experiences to be able to describe their sensations or they may come up with imaginative descriptions. Visual aids or having the child draw what they feel may be useful and valid method to allow children to communicate what they feel in their own "words."

While RLS is typically diagnosed clinically, polysomnography may be performed if the patient is not able to express symptoms in their own words (due to age or language ability) as part of the NIH diagnosis criteria or if another or additional sleep disorder is suspected. Findings on polysomnography that may be expected in a patient with RLS include a prolonged sleep latency and increased rate of periodic limb movements.

Screening or evaluation for potential exacerbating factors, causes of secondary restless leg syndrome, and mimics for RLS is important in making the correct

diagnosis and generating a treatment plan. Many medications have been noted to make RLS worse by modifying dopamine transmission including sedating antihistamines, selective serotonin reuptake inhibitors, melatonin, atypical antipsychotics, and anticonvulsants. Conditions that may predispose patients to iron deficiency include celiac disease, hemoglobinopathies, nutritional iron deficiency, and pregnancy. Musculoskeletal injury or discomfort (injury, cramps, soreness) or neurovascular conditions (neuropathy, radiculopathy) may present with symptoms that may resemble RLS. Finally, it is important to obtain a good social history from the adolescent patient as caffeine, nicotine, and alcohol consumption may also make RLS symptoms worse. Removing these factors or at least insuring that conditions are optimally treated can potentially be sufficient to treat the patient.

Sleep deprivation is another factor that may make RLS symptoms worse. Children with RLS often develop symptoms of behavioral sleep disturbances due to their symptoms such as sleep-onset association insomnia and limit-setting insomnia. Establishing bedtime routines that creates a calming environment (warm baths, physical relaxation techniques, meditation) before bedtime can be helpful in alleviating RLS symptoms. Vibratory counter-stimulation has also been shown to improve symptoms in adults, with an FDA-approved device available.

As iron deficiency is highly correlated with RLS, serum ferritin should be obtained to assess for iron stores if RLS is diagnosed. Levels lower than 50 μg/L suggest a relative iron deficiency and is associated with the onset of RLS, even though levels as low as 22 μg/L are generally considered normal depending on the assay [21]. While both oral and intravenous iron therapies have been shown to improve RLS symptoms in adults, only oral iron repletion has been studied in children. Children are typically given 3–6 mg/kg/day of elemental iron once or twice a day for 3 months. Iron, either as ferrous sulfate or ferrous gluconate, should be given on an empty stomach and with either vitamin C or an acidic liquid such as orange juice to encourage absorption. Repeat serum ferritin level is typically obtained after 3 months of treatment with a target ferritin of >75 μg/L. A gradual taper of iron may begin once target levels have been reached with interval measurements of ferritin to screen for iron overload or return to an iron-deficient state. Constipation and abdominal pain are the most common side effects of iron therapy and can be treated with stool softeners. Other less common but worrisome side effects include dark stool and teeth staining. Iron repletion is contraindicated in children with disorders prone to iron overload such as hemolytic anemia, hemochromatosis, or the need for recurrent transfusion.

Dopaminergic medications such as ropinirole or carbidopa/levodopa have a long history showing efficacy in treating RLS symptoms. Dopaminergic medications have not been well-studied for RLS in children, but side effects in adult patients include nausea, vomiting, hallucinations, and rarely development of obsessive-compulsive behaviors [22]. Most adults treated long term will eventually develop augmentation, which is escalating severity of symptoms due to dopamine receptor downregulation. Patients may also develop rebound symptoms with onset or worsening of symptoms once the medication is cleared of the body.

Calcium channel α2δ-1 subunit ligands such as gabapentin or pregabalin are also approved for RLS in adults [15]. Developed for the treatment of epilepsy, these medications bind to voltage-gated ion channels to decrease presynaptic calcium currents and are also used in treatment of neuropathic pain in adults. While there are no prospective data in children, these ligands have a broad therapeutic profile and are used in the treatment of children with epilepsy. Side effects include sedation and dizziness. Pediatric dosing for gabapentin starts at 5 mg/kg/dose with titration of dose for effect.

Benzodiazepines are often used to treat insomnia and have been used to treat RLS. Rather than decreasing the frequency of sensation/urge to move, it is thought that benzodiazepines result in increased sedation to improve sleep efficiency [23]. These medications can put children at risk for daytime sleepiness, behavior changes, and disruption of nocturnal breathing patterns. There is also the risk of developing dependence or drug subversion that makes benzodiazepine a less attractive option for the treatment of RLS, especially in children. Opioids have been shown to be effective in the management of severe, refractory RLS in adults. Like in benzodiazepines, its use is limited by side effects (respiratory suppression, sedation, behavior changes) as well as dependence risk.

Periodic Limb Movement Disorder

Periodic limb movement disorder (PLMD) is a pattern of periodic episodes of limb movements that occur during and are disruptive to sleep. Periodic limb movements during sleep (PLMS) typically involve extension of the first digit of the foot with flexion of the ankle and knee. The hip may also be involved. These movements may be involved with cortical arousal. PLMS must occur at an increased frequency (more than 5/hour for children and 15/hour for adults), and these leg movements must cause clinically significant sleep disturbance or impaired daytime functioning for a diagnosis of PLMD [1].

Unlike RLS, where there is a conscious effort to move due to an uncomfortable sensation, patients with PLMD are typically unaware of the limb movements or sleep disruption. Despite being a separate disorder, it is thought that both disorders share a common pathophysiology. Both are associated with iron deficiency, respond to dopaminergic medications, and share many comorbidities (ADHD, mood disorder). Having a first-degree relative with RLS increases the risk for development of PLMD [1]. Many children with RLS develop PLMD or noticeable PLMS years before the symptoms of RLS are present [24].

PLMS can represent a normal part of aging as they are uncommon in youth (<40 years) but have increasing prevalence with advancing age, occurring in up to 30% of the general population by age 50 [7]. They are also associated with other disorders such as Parkinson's, REM sleep behavior disorder, narcolepsy, Tourette's, and OSA. Most medications and conditions that can induce RLS symptoms can also induce PLMS.

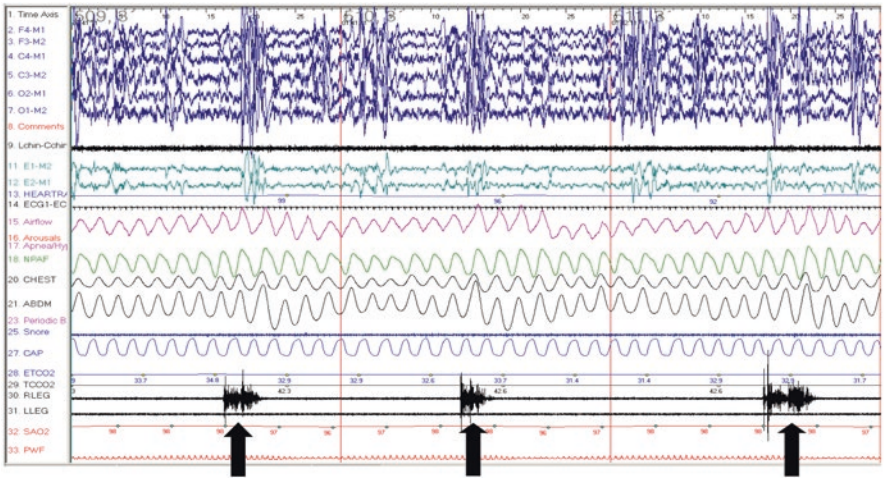


Fig. 10.1 Periodic limb movement during sleep. As seen on polysomnography, multiple 3- to 5-second limb movements (black arrows) in the right leg (RLEG) during this 90-second epoch of non-REM sleep in a child

In addition to frequent leg movements during sleep, complaints of sleep onset or maintenance problems or unrefreshing sleep may predominate the presentation of PLMD. Unlike RLS, which can be diagnosed clinically, PLMD is a diagnosis of exclusion given the association of PLMS with so many different disorders. It is important to know that a diagnosis of RLS or any of these other disorders precludes a diagnosis of PLMD. A sleep study should be done to evaluate the patient for sleep disordered breathing and measure the frequency and timing of movements and the frequency of arousals. PLMS are measured with the tibialis electromyogram leads, with movements typically lasting 0.5–10 seconds (Fig. 10.1). PLMS involve both legs, but movements are not usually simultaneous or symmetrical. PLMS almost exclusively occur during non-REM sleep but are less frequent in stage N3. An elevated PLMS index in the setting of excessive daytime sleepiness is suspicious for narcolepsy. PLMD can be diagnosed in the presence of a sleep-related breathing disorder if PLMS continue despite adequate treatment.

As with RLS, PLMD responds to removal of exacerbating factors such as caffeine, alcohol, and nicotine use. In children, evaluation for and treatment of iron deficiency is considered first-line therapy. Prior to moving forward to other treatment options, other diagnoses should be ruled out, and discussion on the value and trade-off for starting medication for PLMD should be done with the patient and family. The literature is less robust in supporting specific treatment options for PLMD, especially in children [25]. This is partially due to a high background rate of elevated PLMS index in the general adult population and the presence of PLMS in other medical disorders. However, since the diagnosis of PLMD is not common in children and may precede RLS, treatment regimens often follow that of RLS.

Sleep-Related Rhythmic Movement Disorder

Rhythmic movement disorder (RMD) includes repetitive, stereotyped, and rhythmic motor behaviors that involve large muscle groups. Subtypes include body rocking or rolling, headbanging or rolling, as well as a combination of these features [26]. While the movements may occur when the child is awake, they are primarily seen during periods of drowsiness or sleep. Rhythmic movements at sleep onset or during sleep are developmentally normal in infants and children, and RMD is distinguished by significantly interfering with normal sleep, causing significant impairment in daytime function or resulting in injury. Importantly, in children, RMD should be distinguished from similar stereotypical behavior in developmentally delayed children that occurs both during sleep and wake.

The etiology of sleep-related rhythmic movements is not well understood. Rhythmic movements may stimulate the vestibular system, promoting motor development. Sleep-related rhythmic movements typically begin within the first year of life and resolve within a year or two.

The diagnosis of benign sleep rhythmic movement disorder is made clinically. When observed, the frequency of the movements is usually between 0.5 and 2 per second The duration of the cluster of movements is generally less than 15 minutes [26]. In most cases, the child has no recollection of the movements. In children, rhythmic movements seen during sleep are usually seen in N1 or N2 sleep.

No treatment is usually necessary as most sleep-related rhythmic movements resolve spontaneously. In children, it is generally the parent who is concerned about the movements, particularly with headbanging. Treatment is generally directed at reducing the associated noise or preventing injury. In these cases, extra padding on the sides of the crib or at the head of the bed may be used.

Bruxism

Bruxism consists of repetitive clenching or grinding of the teeth and/or thrusting the mandible. Sleep-related bruxism is the presence of regular tooth grinding occurring during sleep that results in either abnormal tooth wear or morning jaw pain or headache.

Sleep-related bruxism is most common in children, affecting 14–17% of the pediatric population. Prevalence decreases with age, affecting about 8.6% adults, with fewer elderly adults affected. A large survey found that 37% of people with sleep bruxism had a first-degree relative who also had bruxism [27], but no genetic variants have been identified. In adults, anxiety, caffeine use, and certain personality types are felt to be predisposing factors for bruxism, but risk factors for children are less clear. Bruxism may occur as soon as the upper and lower teeth have erupted, but it may begin at any age. Bruxism may be associated with medications, including antidepressants and antipsychotics.

A recent meta-analysis of bruxism in children found an association between with snoring, mouth breathing, restless sleep, drooling, prone position, and inadequate

sleep time [28]. There may also be an association in children between sleep-related bruxism and attention deficit hyperactivity disorder. Sleep-related bruxism usually follows arousal and may be associated with an increase in blood pressure and ventilation. Bruxism is more common in N1 or N2 but can be seen in any stage of sleep.

Sleep-related bruxism is usually diagnosed clinically, but it can be reliably recorded using polysomnography. Rhythmic masticatory muscle activity can be observed on polysomnography in healthy people, but individuals with sleep-related bruxism will have intense and frequent jaw muscle contractions during sleep. There can be significant variability from night to night. Unlike in adults, reports of bruxism in children may differ from what is observed by polysomnography. One study of 32 children recruited from an orthodontic clinic found that there was no relationship between questionnaires on tooth grinding and rhythmic masticatory muscle activity [29]. Physical exam may be normal but could demonstrate abnormal tooth wear. The natural history of sleep-related bruxism is felt to be benign, but ongoing problems may lead to temporomandibular joint disorders.

Many people with bruxism will not require any treatment. Avoidance of caffeine and other precipitating drugs before bedtime may reduce bruxism; there is conflicting evidence regarding the efficacy of behavioral therapies. There are a variety of dental devices available for bruxism, including bite splints and mandibular advancement devices. While these devices do not necessarily reduce the amount of bruxism, they may reduce dental damage or discomfort. Soft occlusional splints are often adjustable in growing children. These devices may be contraindicated in children with obstructive sleep apnea or seizures.

Benign Sleep Myoclonus of Infancy

Benign sleep myoclonus of infancy (BSMI) is a relatively rare disorder in infants less than 6 months of age that is characterized by repetitive myoclonic jerks that occur exclusively during sleep. The movements are typically bilateral and may involve the whole body, just the limbs, trunk, or rarely the face, and may occur in any stage of sleep [30]. Typically, BSMI is seen in full-term, neurologically normal infants, but there has been an association described with neonatal opioid withdrawal. BSMI is twice as common in boys as girls. The incidence has been estimated to be 3.7 per 10,000 live births. One study reported that in the majority of cases, symptoms began within the first week of life and were most commonly generalized, symmetric, synchronous jerks [31].

The pathophysiology of BSMI is not completely understood. One theory is that the features are due to immature myelination of the descending pathways of the cervical spine. Another possibility is that transient neurotransmitter abnormalities in an immature subcortical structure may be responsible. Multiple cases of benign myoclonus in infancy have been reported in families, but a hereditary mechanism remains unknown [32].

BSMI may be part of a spectrum of benign neonatal and infantile convulsions, sharing many features with non-epileptic myoclonic attacks in infancy, but only

occurs in the sleeping infant. Both are defined by a benign course and normal EEG and usually occur in otherwise healthy infants. Importantly, BSMI should be distinguished from infantile spasms, which demonstrate hypsarrhythmia on EEG and usually include a characteristic head and lower extremity flexion and upper extremity extension. Additional diagnoses to consider include sleep starts, which are typically isolated and only occur either at sleep onset or upon awakening.

While there is limited prospective data, there are no complications known to occur from BSMI, and it will usually resolve by 6 months of age or before. Therefore, reassurance with close follow-up is appropriate. Neither holding the limbs during episodes nor antiepileptic drugs has been shown to effectively shorten the course.

Isolated Symptoms and Normal Variants

Hypnagogic Foot Tremor/Alternating Leg Muscle Activation

Hypnagogic foot tremor (HFT) is a rhythmic movement of the foot or toes that occurs during sleep transition. Children with HFT can be observed to rhythmically move their toes and/or feet at sleep onset. On polysomnography, at least four activations occur in a single leg, typically lasting 10–15 seconds or longer [26]. In most cases, the movements are subtle but in some cases can be more dramatic.

Alternating leg muscle activation (ALMA) is noted when there is alternating brief activation of the anterior tibialis muscles during sleep or arousal. ALMA can sometimes be observed clinically during sleep but other times is only detected by surface EMG testing on polysomnography. ALMA may occur with the use of selective serotonin reuptake inhibitors or in conjunction with other sleep disorders like OSA [33].

HFT and ALMA are not felt to be associated with any adverse consequences and are generally incidental findings on polysomnograms done for other reasons. While primarily reported in adults, HFT and ALMA have been described in older children as well. Because of the similar length and frequency of the movements (1 to 2 Hz) and the similar demographics of those affected, ALMA and HFT may represent different presentations of the same type of movement. Possibly, ALMA and HFT could be related to rhythmic movement disorder. In children, these movements usually need to be distinguished from periodic limb movements in sleep.

Sleep Starts

Hypnic jerks, also known as "sleep starts," usually consist of a single sudden brief muscle contraction of one or more body section at sleep onset. Sleep starts may be accompanied by a sensation of falling or an auditory or visual hallucination that can sometimes be intense or uncomfortable. The pathophysiology is unknown, but the "start" may be a response to the sensory component of the event [34]. Hypnic jerks are very common, usually occurring sporadically in children of all ages. Hypnic jerks may be exacerbated by the use of caffeine or other stimulants, as well as stress or

intense physical activity before bedtime. Although considered physiologically normal, they can lead to delayed sleep onset in extreme cases. In neurologically impaired children, sleep starts occurring in clusters have been described and need to be distinguished from seizures [35].

Catathrenia

While actually classified as a sleep-related breathing disorder, catathrenia has no known association with any respiratory abnormalities. Catathrenia typically involves a deep inspiration followed by prolonged expiration with a monotonous groaning sound, typically during REM sleep. The mechanism of sound is felt to be due to subtotal closure of the glottis. The prevalence of catathrenia in children is unknown, but it is felt to be rare and has been described in children as young as 4 years [36]. Catathrenia has been associated with sodium oxybate use in patients with narcolepsy [37]. It is felt to be benign and typically does not warrant treatment.

In summary, while many sleep-related movement disorders are benign and require no specific therapy, others can be disruptive to sleep and may require treatment. These disorders are important to understand as they may mimic more serious conditions such as epilepsy. More research is needed to better understand how some movement disorders specifically affect children.

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Evaluation and Management of Allergic Disorders Related to Sleep Pathology

11

Innessa Donskoy and Stephen H. Sheldon

Sleep is a unique experience that humans spent a substantial portion of their lives participating in, with little recollection or perceived importance given to it, unless it is disrupted. The human body runs on almost 24 hour circadian rhythms that time sleep, wake and a multitude of other physiologic processes with remarkable regularity [1]. Ultradian rhythms throughout the night guide the brain through lighter stages of non-REM sleep (N1, N2), into more restorative deep slow-wave sleep (N3), and then into rapid eye movement (REM) or dream sleep. Sleep disruption causes fragmentation in the ultradian rhythms of nocturnal sleep and further decreases the arousal threshold. This can lead to excessive daytime sleepiness and all of the impacts this has on performance, safety, mood, and overall quality of life. Possible disruptors to sleep are myriad but often include those of atopic origin. Asthma, allergic rhinitis, atopic dermatitis, and an overall allergic predisposition may lead to disruption in many ways. Asthma affects 7.6% of adults and 8.4% of children in the United States [2]. Approximately 40% of asthmatic patients report nocturnal awakenings at night and increased daytime sleepiness [3]. Allergic rhinitis is a common disorder as well, affecting between 10% and 20% of the US population [4]. Patients who report allergic rhinitis and nasal congestion are 1.8 times more likely to have moderate to severe sleep disordered breathing [3]. Associated daytime sleepiness and decreased quality of life have been reported in patients with allergic rhinitis and are often linked to unexpected

I. Donskoy
Department of Pediatric Sleep Medicine, Advocate Children's Hospital, Park Ridge, IL, USA

S. H. Sheldon (✉)
Departments of Pediatrics & Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Sleep Medicine Center, Division of Pulmonary and Sleep Medicine, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: ssheldon@luriechildrens.org

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arousals at night [5]. The prevalence of atopic dermatitis is approximately 7.2% and may be underestimated given the reluctance to seek medical care for sometimes mild symptoms [5]. However, even controlling for associated allergic disorders, atopic dermatitis alone can lead to poor sleep and impaired daytime functioning [5]. Atopic issues are well-established disruptors of sleep quality via various means. Mechanisms by which allergic and sleep disorders affect one another are complex and not clearly understood. Nonetheless, effects can be investigated by looking at nocturnal sleep disruption, immunologic reactivity, and circadian mechanisms. Just as atopic disease can predispose an individual to disordered sleep, disorders relating to sleep also play a role in the onset and overall course of atopic disease processes, as addressed elsewhere in this volume. Not addressing sleep-related issues in management of allergic disorders negates the importance of the two-way interaction.

Respiratory Perspective

Individuals with fragmented sleep are at an increased risk for worsened cognition, declining school and work performance, psychological disorders, obesity, accidents, and injuries [6, 7]. Even individuals who are self-reported good sleepers can have sleep disruption from stress [8]. A potential source of physical and psychological stress may be allergic disease [9]. It has been previously shown that disordered sleep may not only worsen allergy symptoms in adults but can cause new-onset allergic symptoms in children [10]. Sleep can be disrupted in a multitude of ways, but often the disruption is considered of respiratory etiology. Sleep disordered breathing constitutes a continuum of diagnoses varying in severity from mouth breathing due to nasal obstruction, primary snoring, upper airway resistance syndrome (UARS), and obstructive sleep apnea (OSA). OSA is a sleep disorder where recurrent airway obstruction or partial obstruction leads to decreases in oxygen saturation, carbon dioxide retention, and sleep fragmentation (ranging from microarousals to complete waking). Brief waking helps restore airway patency and normalize oxygen and carbon dioxide levels but inevitably leads to sleep fragmentation and excessive daytime sleepiness [11]. A study that looked at habitual snoring in the pediatric population demonstrated that having a family history of atopy in combination with snoring predisposed younger children to obstructive sleep disordered breathing [12]. At younger ages rhinitis and wheezing (a surrogate for asthma at ages when pulmonary function testing cannot be performed) were associated with habitual snoring [12]. At older ages, an official diagnosis of asthma, recurrent URIs, and even eczema were correlated with snoring [12]. A Brazilian study in 2017 looked at sleep disruption in children with a diagnosis of allergic rhinitis (AR) compared to healthy controls. Twice as many children in the AR cohort met the criteria for disordered sleep, the odds increasing even further with poorly controlled symptoms and disease severity [13]. Subset analysis showed a statistically significant increase in “parasomnias” (defined by the group as sleep terrors and waking from nightmares but also included nocturnal enuresis and restless appearing sleep),

respiratory disorders (loud breathing, snoring, or witnessed apneas), and daytime sleepiness.

There is a proposed mechanism of obstruction by which allergic rhinitis is thought to affect breathing in sleep. The pediatric airway functions as a Starling resistor, in that the potentially collapsible segment of the airway (the pharynx) is surrounded by upstream (nasal) and downstream (hypopharynx) areas whose pressures can be affected by multiple factors (hypotonia, sedation, obesity, edema, glandular obstruction, etc.) (Fig. 11.1) [14]. Collapse occurs when the pressures surrounding the pharynx exceed the critical closing pressure (Pcrit) within it. Upon inspiration, downstream pressure decreases allowing for a pressure gradient to promote air entry. The amount of airflow which ultimately occurs is then determined by the gradient between the upstream and collapsible areas. Increased nasal resistance

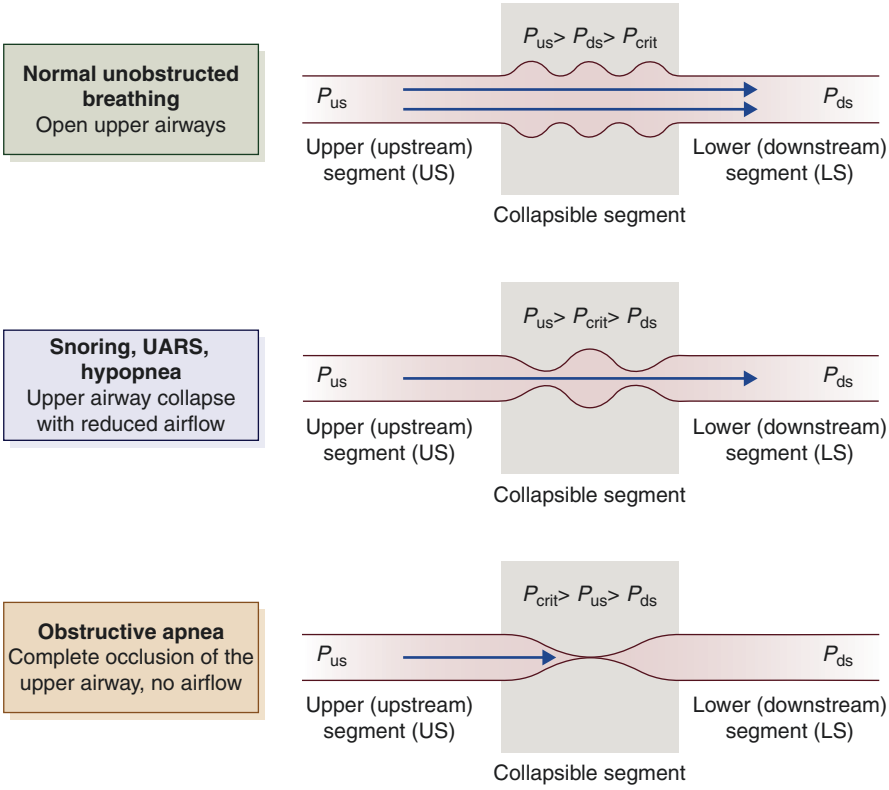


Fig. 11.1 The upper airway can be represented as a mechanical analogue of the Starling resistor model, consisting of a rigid tube with a collapsible segment. The collapsible segment has no resistance but is subject to the surrounding pressure, Pcrit. Collapse occurs only when the surrounding pressure exceeds the downstream pressure and inspiratory airflow decreases compared to normal unobstructed breathing. Complete occlusion occurs when Pcrit exceeds both the upstream and downstream pressure. (From Kirkness et al. [14]. Copyright © 2006. Karger Publishers, Basel, Switzerland, with permission.)

from congestion and inflammation results in negative intraluminal pressure that can surpass the critical closing pressure of the airway and lead to upper airway collapse. An older study was able to show that nasal resistance in patients with OSA is higher than in control subjects [15]. While there have been studies which suggest this mechanism, the data are somewhat controversial [16, 17]. Disparities may be explained by the heterogeneity of OSA: at times due to anatomy, muscle function, a low arousal threshold, or unstable control of ventilation [18]. While humans have one lower airway, there are two entry points: nose and mouth. Theoretically, inflammation or obstruction in one area may have impacts on the other. While allergic rhinitis resides in the nasal passage ways, tonsillar hypertrophy affects the oropharynx. With nasal obstruction, air is unable to enter and flow through this ideal laminar path, so the mouth is chosen instead. This is a physiologic reaction, but not an ideal substitute. Mouth breathing may be the first reported symptom in disordered breathing of sleep, noted even incidentally. However, mouth breathing alone has also been shown to have a negative impact on pulmonary function testing [19], irritate the airway due to cold dry air [20], and increase the inhalation of small particles including indoor aeroallergens [21]. Allergic rhinitis can be an easily identified culprit for mouth breathing. However, in a questionnaire-based study of adult subjects in Japan, mouth breathing was determined to be a risk factor for asthma independent of allergic rhinitis, pediatric asthma, or eosinophilia. When mouth breathing and allergic rhinitis were both reported, the odds ratio of a subject having asthma increased twofold [22]. Obstructive sleep apnea is a known correlate of poor control of asthma [23]. The presence of nocturnal asthma symptoms can lead to numerous awakenings at night [24]. In children, associations have been demonstrated between the number of nightly awakenings and poor school performance, school absences, and behavioral problems [25–27]. Napping is more common in children with asthma versus healthy controls [28] which is reflective of excessive daytime sleepiness. While there is a predisposition of patients with asthma to develop sleep disordered breathing (SDB), in children who were already diagnosed with SDB, the odds ratio of having severe asthma was increased by 3.62 [29], suggesting bidirectionality. Disrupted sleep can cause asthma symptom exacerbation, while improved sleep may mediate symptoms. A self-reported increased quantity of sleep demonstrated an improvement in peak expiratory flow in children with asthma [30]. However, timing and causation is challenging to tease out. It was previously shown that obstructive sleep apnea prevalence is increased in asthmatics and that control of the OSA allows for improved control of asthma symptoms in children [12, 13, 18, 25, 26]. In a recent study, the presence of asthma history was associated with significantly more adenotonsillar regrowth [31], leading to increased airway obstruction and the potential for respiratory-driven sleep disruption, suggesting a two-way interaction. In a longitudinal twin study [32] where children were questioned at two points (around 8 and then 13 years of age), some insight into this relationship was revealed. Being overtired, regardless of the reason, at younger ages was associated with asthma and rhinitis at older ages. If asthma symptoms were controlled, the correlation disappeared (although having symptoms of asthma at a younger age was associated with being overtired, having a short sleep time, and trouble sleeping later

on in life). However, control of rhinitis symptoms was irrelevant, and disrupted sleep was an independent predictor of developing or continuing to endorse rhinitis symptoms.

Fortunately, the treatment of sleep disordered breathing, as well as that of allergic disorders, is well studied and regimented. A stepwise approach to investigating sleep disordered breathing [33, 34], includes polysomnography to determine the severity. If obstructive sleep apnea is diagnosed, it can be further classified into mild, moderate, or severe. Depending on severity and comorbidities, at least in pediatrics, often removal of the tonsils and adenoids (adenotonsillectomy, T&A) is pursued, with the assumption that airway obstruction is a prominent mechanism for SDB. Uncontrolled allergy symptoms can lead to congestion and inflammation that will further impair nocturnal airflow, and OSA alone can feed back causing sleep disruption worsening allergic disease burden. It is to be concluded that optimizing the treatment of allergic and sleep disorders is imperative to have the best overall results for both disease processes. Studies have looked at the use of montelukast and intranasal steroids in the postoperative period for treating residual OSA after adenotonsillectomy. In theory, these anti-inflammatory medications systemically or locally (respectively) serve to decrease the size of glandular tissue which may obstruct normal breathing [35]. There have been demonstrated improvements in overall outcome after T&A with this adjunctive treatment of OSA, but this may have been treating an underlying allergic rhinitis which would otherwise have predisposed the patient to adenotonsillar regrowth [36]. Regardless, the importance of controlling allergic rhinitis is paramount for the short- and long-term efficacy of the surgical treatment of pediatric OSA. Intranasal corticosteroids can improve the quality of sleep and reduction in symptoms in patients with OSA [37, 38]. While corticosteroids have been shown to improve symptoms, sleep, and daytime energy in patients with AR [38, 39–41], sedating medications such as antihistamines in the daytime may actually worsen already poor performance in school due to their sedating side effects. Caution should be taken when trying to improve allergic symptoms, not to compound further daytime sleepiness in a child who may likely also have a sleep pathology.

Dermatologic Perspective

An increase in respiratory events from nasal or oropharyngeal obstruction is not the only way in which allergic disease can disrupt sleep. Eczema (atopic dermatitis) is an inflammatory skin disorder that manifests as pruritus which can lead to distress during the day and nighttime [42]. In the past, actigraphy has shown that patients with eczema move more at night, suggesting less time in sleep and more in wake, leading to decreased sleep efficiency [43, 44]. While it may be tempting to attribute this to arousals related to itching due to pruritus, subjects with eczema still show decreased sleep quality even with well controlled symptoms [45]. Concurrently having a diagnosis of eczema and a sleep disorder increases the risk of psychological comorbidities as well as outcomes of excessive daytime

sleepiness such as motor vehicle accidents and injury [8, 16]. A large study in adults in 2015 found that a reported eczema diagnosis in the last year was associated with a higher odds ratio of a shorter or longer than average sleep duration, even when controlling for other allergic disease [5]. While a short sleep duration suggests fragmented/disrupted sleep, a long sleep duration may be a downstream manifestation of disrupted sleep (excessive sleepiness) as well as potentially being due to the use of sedating antihistamines for symptom control. Upon sub-analysis, there were two groups of patients with eczema: ones with other sleep comorbidities including insomnia, fatigue, and daytime sleepiness and another with only a higher probability of insomnia [5]. The question of why some sufferers of eczema have a more drastic impact on their sleep and energy is an intriguing one, suggesting that there may be a way to individualize therapy. Similar to varying OSA phenotypes [46], there may be differences among the different types of eczema [47] that have a range of effects on sleep and, in turn, daytime functioning. There is a significant two-way interaction noted between sleep and atopic dermatitis. While the symptoms of eczema can disrupt sleep, complaints of daytime sleepiness, insomnia, but more notably the combination of the two, increase the odds ratio of having eczema by a factor of three [5]. Perhaps there is a downstream effect from poor-quality sleep which can precipitate eczema in susceptible individuals.

Immunologic Perspective

It becomes clear from looking at mechanical disruptors of sleep and physiologic triggers for asthma, allergic rhinitis, and atopic dermatitis that there are other, more subtle, forces at play in how the pathologies of sleep and allergic disease correlate. Fatigue, even in the absence of disordered sleep, has been reported in association with allergic disease [48, 49], and teasing apart fatigue from the lack of quality sleep is challenging. Determining the chronologic relationship between allergic disease and sleep disruption leading to daytime sleepiness is also not simple. Children with positive allergy tests are more likely to have obstructive sleep apnea [50]. It is theorized that an allergic disease process leads to growth of lymphoid tissue (like tonsils and adenoids) increasing their size and risk of obstruction leading to respiratory symptoms. Recent analyses have added more evidence to this hypothesis, showing that the presence of reported history of allergic disease in young patients, and even more so in older children, is a risk factor for adenotonsillar regrowth after surgery [31]. This suggests that the development of allergic disease and exposure to specific triggers has long-term outcomes for the quality of sleep these patients will have. However, upon immunologic analysis of tissue from subjects who had adenotonsillar regrowth, there was no significant difference in the amount of total leukocytes and CD4+ T cells [31]. There was a significant increase in the serum IgE, suggesting that although the amount of leukocytes is not significantly different, their function and downstream production of inflammatory mediators certainly are. Interestingly, there was also a decrease in FoxP3 and an increase in GATA3+ in tissue from subjects with adenotonsillar regrowth. FoxP3 (forkhead box P3) is a transcription factor that

promotes the differentiation of Th0 cells into regulatory T cells (Tregs) which are integral to the suppression of immune reactions [51]. Interestingly, sleep deprivation alone can disrupt regulatory T cell function [52]. On the other hand, GATA3+ is a transcription factor expressed by a specific type of helper T cells (Th2) which feeds back to help more Th0 cells differentiate into the Th2 subtype [53]. This shift to more Th2 CD4+ cells is thought to be the driving factor behind allergic disease (Fig. 11.2) [54, 55]. It is this suppression of mediation from FoxP3 as well as a GATA3+-driven increase in the Th2 cell type which promotes allergic reactivity, inflammation, and possibly adenotonsillar regrowth. This may lead to overall airway inflammation and respiratory disruption [56]. It may also promote the release of downstream cytokines, which have been correlated with decreased sleep latency (a sign of increased sleepiness) as well as increased REM latency and less time in REM sleep (a sign of poor-quality sleep) [57]. This fits with previously self-reported difficulties with sleep onset, maintenance, and sleep disruption in patients with allergic rhinitis [58]. It suggests that something inherent in the allergic process can decrease sleep quality and impact daytime functioning. An exciting new research avenue being explored is the role of yet another CD4+ cell type, the Th17 subset. These cell types play an important role in promoting allergic and autoimmune disease and have been shown to be correlated with subjects who have sleep disordered breathing from OSA [59]. It is theorized that repeat infections or exposures to infectious triggers promotes Th17 recruitment and that, over time, reactive tissue increases in size, causing sleep disordered breathing [59]. However, the downregulation of Tregs from sleep deprivation further skews the Th17/Treg ratio and leads to an even further unchecked inflammatory cascade, which impairs control of systemic allergic symptoms, leading back to increased physical impedance of nocturnal breathing needed for quality sleep.

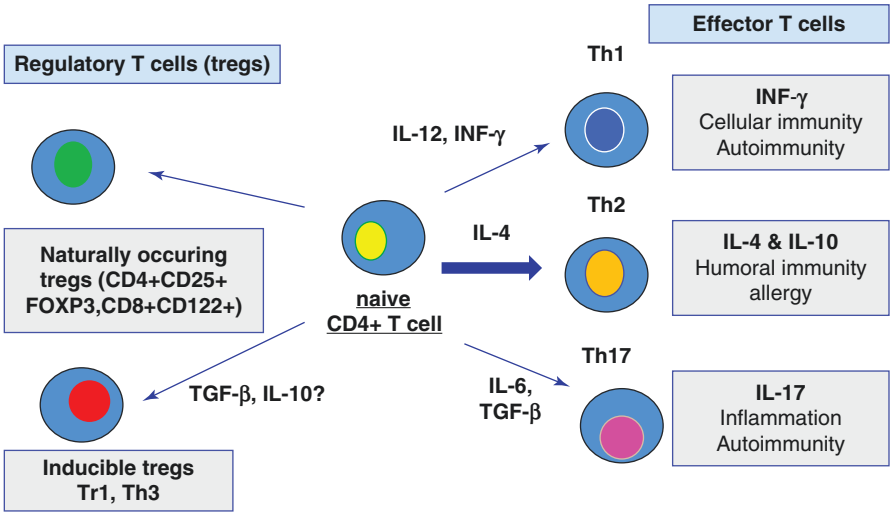


Fig. 11.2 The differentiation of CD4+ cells into specific T cell subsets. (From Rydzewska et al. [70], with permission.)

Circadian Perspective

The circadian rhythms that regulate sleep also regulate many other bodily processes including hormone synthesis [1]. The nadir of cortisol secretion is in the night and this dip alters the inflammatory pathway (Fig. 11.3) [60]. Many allergic processes are prevented and treated with exogenous steroid to modulate the immune reaction, and the absence of endogenous cortisol in the night often leads to peaks of symptoms of asthma exacerbations and allergic rhinitis [61, 62]. In subjects with atopic dermatitis, there is also a rhythm to transepidermal water loss which has a peak in the evening, and this topical dehydration may lead to increased pruritus, causing sleep onset issues and sleep maintenance insomnia [63]. Histamine, a mediator of allergic reactions, is present in the wake state, and targeted therapies may promote drowsiness and actually treat insomnia. As allergic symptoms flare in the night, with more histamine release from mast cells, this disrupts sleep at the central nervous system level [64] and causes a waking state (Fig. 11.4). Some early pharmacologic studies have begun to utilize circadian rhythms in the optimal dose timing for medication [65], and this may be a future avenue to explore in the treatment of allergic disease. Interestingly, while there is a circadian rhythm to certain cytokines such as IL-2, there is more of a sleep-dependent rhythm to the expression of regulatory T cells that

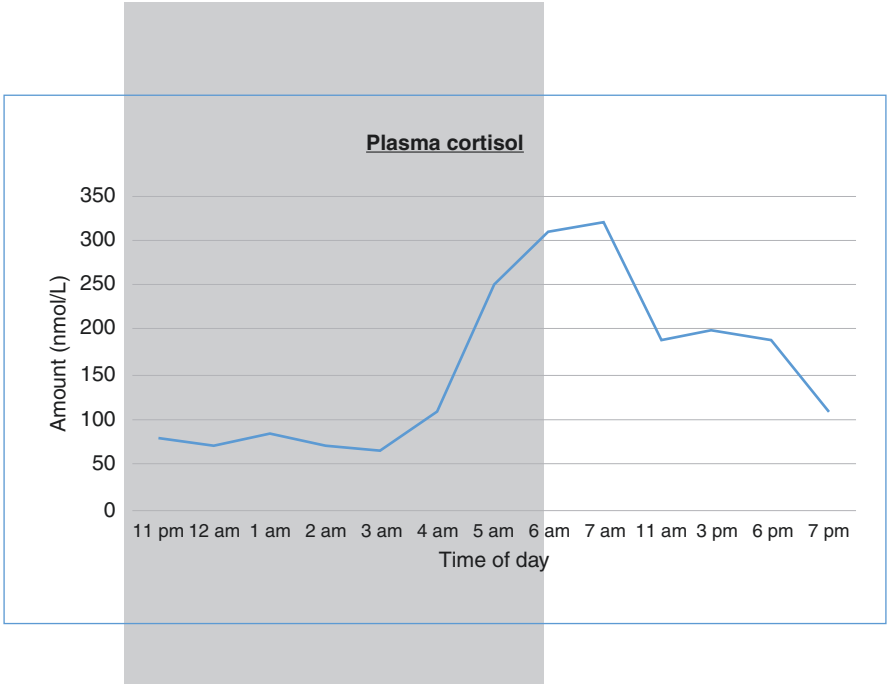


Fig. 11.3 The mean changes in human plasma cortisol over a 24-hour period, with a nadir in the night. (Adapted from Axelsson et al. [71].)

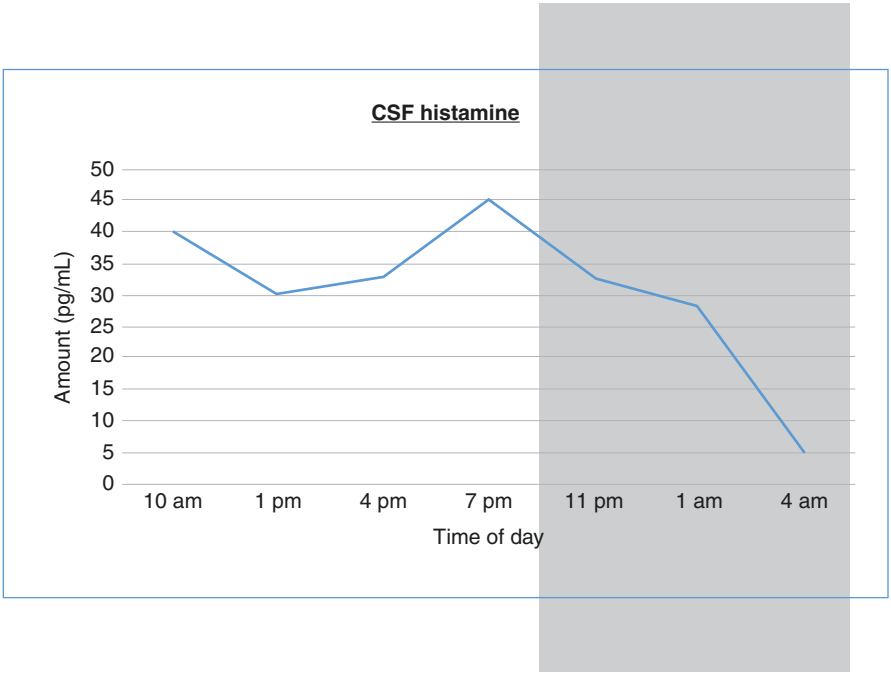


Fig. 11.4 The mean changes in CSF histamine over a 24-hour period in squirrel monkeys, who have a similar consolidated active/wake state in the daytime. A nadir in histamine can be seen during sleep. (Adapted from Zeitzer et al. [72]. Reprinted by Permission of SAGE Publications, Ltd., with permission.)

may mitigate the inflammatory cascade [52]. This suggests that although some of the fluctuations of inflammation are circadian and beyond an individual's control, ensuring quality and quantity of nocturnal sleep could be a big factor in easing symptom burden.

Positive Perspective

There has been a largely negative focus on the relationship between the presence of disordered sleep and allergic disease. However, some recent literature has shed light on another perspective. Narcolepsy is a disorder of sleep dysregulation in both sleep and wake which manifests as excess daytime sleepiness, hypnagogic and hypnopompic hallucinations, sleep paralysis, and in certain types, cataplexy [66]. On an MSLT (multiple sleep latency test), patients will characteristically have a short mean sleep latency over a series of daytime naps, even after a full night of sleep, and at least two sleep onset REM periods (SOREMPs) during those naps. Type 1 narcolepsy (with cataplexy) pathophysiology which involves loss of orexin (also known as hypocretin)-producing neurons in the lateral hypothalamus, at times without a clear cause. Type 2 narcolepsy has an even more elusive

pathophysiology, with no objective decrease in orexin nor any presence of cataplexy symptoms. There is a strong argument made for an underlying immunologic cause of narcolepsy, especially given its seasonal variation, associations with ASO titers, and an impressive peak during the H1N1 influenza outbreak in 2009 [67]. Both types of narcolepsy have a strong association with the HLA-DQB1*0602 allele but also with a demonstrated presence of Th2 lymphocytes [68]. When activated, T cells have the ability to attack targets and damage cells such as in the lateral hypothalamus, a theorized immunologic mechanism behind narcolepsy type 1 [69]. However, in a large multicenter study looking at over 400 cases of pediatric narcolepsy, subjects with type 1 narcolepsy had a lower frequency of asthma and allergic rhinitis (although not atopic dermatitis), suggesting a shift away from a Th2 cell type balance. Those subjects with concurrent type 1 narcolepsy and a diagnosed allergic disorder had longer mean sleep latency on MSLT, and the number of SOREMs was decreased, suggesting a milder phenotype. In other words, the presence of allergies (the shift toward more Th2) was a mitigating factor in the severity of the narcolepsy with cataplexy. This adds to the complexity of the interplay between sleep and allergic disease, whereas they are thought to impede the other, this is an example of symptom reduction. This is important in that it may make symptoms more subtle in new-onset narcolepsy if there is an underlying allergic condition. One may need to have a higher index of suspicion regarding new symptoms of fatigue or sleepiness in a patient with known allergic disease.

The interplay between allergic disease and sleep pathology is intricate and likely bidirectional. There is a great deal of data demonstrating the impact that respiratory and dermatologic symptoms of specific allergic diseases such as asthma, rhinitis, and dermatitis have on sleep efficiency. Disruption to sleep, in turn, can cause a worsening of allergic symptoms. There is also a cascade of inflammatory players that comes along with allergic conditions (regardless of whether or not symptoms are controlled) which is disruptive to sleep and can feed back to exacerbate overall inflammation and allergic symptoms. Not to be excluded are the notable circadian and sleep/wake patterns of cortisol and histamine, respectively, which can provoke or protect against allergic flares. Some early pharmacologic studies have begun to utilize circadian timing in optimal dose administration [1], and this may be a future avenue to exploration of the treatment of allergic disease. While worsening of allergic or sleep pathology will usually lead to a negative shift in the other, there is also an unexpected attenuation of symptoms of a certain type of narcolepsy in the presence of allergic disease. Finally, adding to this complexity is the fact that, as with any physiologic balance, there is a great deal of individual variation. Some patients with atopic dermatitis seem particularly sensitive to sleep disruption, and others are more resilient to the impact their disorder has on sleep. Some patients with sleep disordered breathing, even after surgical intervention, may or may not have glandular regrowth due to persistent inflammatory markers, while others recover completely even with a personal reported history of atopy [66]. Individualization will be a key moving forward, in understanding the specific sleep and allergic

issues that patients are suffering from, being conscientious in screening for one when the other is present, and tailoring management to ensure the optimization of both types of disorders.

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Part III

Asthma

Sleep-Related Disturbances Commonly Associated with Asthma

12

Sofia Konstantinopoulou and Ignacio E. Tapia

Nocturnal Asthma: Definition and Pathophysiology

Asthma is a chronic inflammatory disease of the lower respiratory tract characterized by bronchial hyperreactivity and episodic partially reversible lower airway obstruction. Asthma is one of the most common chronic respiratory diseases of childhood [1], affecting 9.3% of children 14 years of age and younger [2]. Despite evidence-based guidelines for the evaluation and treatment of asthma, the impact of asthma on quality of life and health cost of patients is very high [3–6].

Frequency of missed sleep due to asthma symptoms is commonly used as indicator of asthma morbidity [7]. Difficulty initiating or maintaining sleep, related to asthma symptoms, may in fact reflect poorly controlled asthma. For instance, a child with asthma may wake up often during sleep either because of persistence of symptoms [8], inappropriate medication control [9], lack of adherence to the medical regimen, or exposure to household environmental allergens [10]. Many asthmatics experience worsening of their symptoms at night, and up to 90% report wheezing or nocturnal cough [11]. These symptoms may be related to functional changes in ventilation during sleep as asthmatics have greater loss of functional residual capacity (FRC), peak expiratory flow rates (PEFR), and tidal volume during sleep than normal subjects [12]. The severity of the morning decline in PEFR is closely correlated with higher lower airway resistance and its duration during sleep. Other

S. Konstantinopoulou
Division of Pulmonary Medicine, Department of Pediatrics, Sheikh Khalyfa Medical City, Tibbiyya, Abu Dhabi, United Arab Emirates

I. E. Tapia (✉)
Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Sleep Center, Division of Pulmonary Medicine, The Children's Hospital of Philadelphia, Philadelphia, PA, USA
e-mail: tapia@email.chop.edu

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factors which contribute to the pathophysiology of nocturnal bronchoconstriction include decreased inspiratory muscle activity, direct effect of cold air on airway tone, decreased mucociliary clearance, enhanced bronchial hyper-responsiveness due to increased parasympathetic tone [13], and hormonal changes such as increased levels of histamine [14].

Nocturnal Asthma Related to Sleep Disturbances

Patients with nocturnal asthma symptoms are likely to have frequent arousals during sleep and report worse sleep quality [15]. For example, asthmatic adults compared to controls have reported less sleep time and sleep efficiency and greater time awake after sleep onset (WASO) [16]. In another study performed in adults, 12 asthmatic volunteers with nocturnal symptoms were compared with 10 age-matched control subjects. Each subject spent two consecutive nights in the sleep lab; the first night was considered acclimatization to the laboratory environment. The data collected from the second night indicated increased wake time, decreased mean sleep time, and increased number of awakenings in asthmatic subjects compared to normal subjects. There was no significant difference in sleep latency and percentage of REM sleep. However, there was markedly decreased slow wave sleep, which was replaced by stage 2 and stage 1 sleep, in the asthmatic group [17]. Several studies have shown similar findings in children with asthma. For example, in a sample of urban children with asthma, night waking from asthma occurred in 40% of the sample during a 1-month period [18]. Moreover, the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study provided a better example of sleep disturbances related to asthma. Parents of 2529 children aged 11 years who participated in PIAMA reported asthma symptoms such as wheezing, dyspnea, prescription of inhaled corticosteroids, and asthma diagnosis; and children reported subjective and objective characteristics of their sleep such as bedtime, rise time, sleep quality, and daytime sleepiness [19]. Data were analyzed based on asthma symptoms. Children without asthma symptoms rarely reported daytime sleepiness in contrast to children with asthma symptoms (43% vs. 29.2%, $p < 0.01$). Importantly, results were not confounded by sex, age of the child, parental educational level, or smoking inside the house [19].

Similarly, in a cohort of 487 adults with asthma, there was a positive correlation between sleep quality, asthma control, and quality of life [20]. Daytime cognitive performance and objective overnight sleep quality have also been reported to be poor in adults with nocturnal asthma as compared to a control population [21]. Importantly, this study provided evidence that improvements in sleep quality and sleepiness were significantly associated with improvements in asthma control and quality of life. Another study investigated the level of asthma control in real life and the relationship between Asthma Control Test (ACT) scores and sleep disturbances [11]. One hundred twenty-two patients aged 15–75 years presented for a routine asthma visit and were asked to complete the ACT questionnaire and to answer five questions regarding their sleep quality. Researchers found that asthma control was

unsatisfactory in 44% of the sample. The level of asthma control appeared to be inversely correlated to the presence and impact of sleep disturbances in comparison to uncontrolled subjects, suggesting that participants with good control reported less frequent and less severe sleep disturbances compared to poorly controlled subjects [11]. A double-blind placebo-controlled trial of the long-acting inhaled beta-2 agonist salmeterol administered morning and evening showed that participants on a higher dose of 100 mcg spent more time in slow-wave sleep versus participants on a lower dose of 50 mcg versus participants on placebo ($p < 0.02$, $p < 0.05$) [22]. This study suggested that better control of asthma symptoms, as reported by participants receiving a higher salmeterol dose, may improve quality of sleep. The physiological and temporal relationships between asthma control and quality of sleep need to be addressed in further clinical trials that should not only include subjective assessment of asthma control and quality of sleep based on questionnaires but also objective measures such as spirometry and actigraphy. Indeed, Meltzer et al. recruited ten adolescents with asthma (60% female; 60% Caucasian; mean age, 13.7 years; range, 12–17) who completed a 3-week randomized, crossover sleep manipulation protocol that allowed them a 5-night deficient sleep opportunity of 6.5 hours in bed or a healthy sleep opportunity of 10 hours in bed [23]. Daily reports of sleep patterns and asthma symptoms, actigraphy, daily PEFR, weekly spirometry, and exhaled nitric oxide were collected. In terms of asthma-related outcomes, this study showed significant changes in both objective and subjective measures of daily lung function. Specifically, significant differences between the experimental study weeks were found. Adolescents in the deficient sleep week arm had a lower morning FEV_1 of 14% ($p = 0.03$), lower morning PEFR of 6% ($p = 0.05$), and greater overnight PEFR changes ($p = 0.07$) compared to those in the healthy sleep opportunity week. This pilot study using an experimentally manipulated sleep protocol was the first to suggest that deficient sleep may contribute to negative asthma outcomes in children, thus showing a bidirectional relationship between sleep duration and asthma [23].

Sleep Disturbances Despite Adequate Asthma Control

Although nocturnal exacerbations may indicate inadequate asthma control and can disturb sleep, poor sleep has also been reported in patients with well-controlled asthma suggesting that poor sleep may be independent from nocturnal asthma symptoms [11, 24]. This could be due not only to the potential effects of common comorbidities that can disturb sleep, such as sleep-disordered breathing (SDB) and gastroesophageal reflux disease (GERD) as discussed later in this chapter [25], but also to poor sleep itself that can affect asthma control as an independent factor. In fact, a cross-sectional study examined the association between sleep quality, asthma control, and quality of life after accounting for SDB and GERD in non-severe (NSA) and severe asthmatics (SA) [26]. Data from 60 normal controls, 143 NSA, and 79 SA were examined. Those who reported using positive airway pressure therapy or those who were at high risk for SDB were excluded to minimize the role of SDB as a confounding sleep disruptor. Both SA and NSA groups had poorer sleep quality than

controls, with SA reporting the worse sleep quality of the three groups. Poor sleep quality in both NSA and SA was associated with worse asthma control and quality of life after controlling for age, BMI, and other covariates such as GERD and allergic rhinitis. However, the key point of this study was that the majority (88–100%) in the NSA and SA groups still reported poor sleep quality in the absence of nighttime asthma disturbances. A plausible explanation for disrupted sleep in well-controlled asthmatics may be a coexisting sleep condition, such as insomnia, which is at least partly independent from nocturnal asthma symptoms. The development of insomnia can involve several etiologic factors, including predisposing factors, precipitating factors, and perpetuating factors [27]. Predisposing factors increase the individual's vulnerability to develop insomnia and can include personality traits such as anxiety or hyperarousal and/or genetic factors such as female sex, aging, or family history of insomnia [28]. Precipitating factors such as stressful life events and health and psychosocial problems can trigger the onset of insomnia. For example, asthma itself can serve as a precipitating factor as nocturnal asthma attacks, nighttime inhaler use, and medication use during sleep can be stressful. Perpetuating factors contribute to self-sustained sleep problems [26]. In the case of asthma, anxiety about a possible attack during the night could contribute to chronic insomnia.

Children living in urban environments have been reported to have many risk factors for disrupted sleep including environmental disturbances, stressors related to ethnic minority status, and higher baseline levels of stress and anxiety [29]. Parents of 147 children aged 6–13 years completed measures of asthma morbidity and missed sleep, parental quality of life, and a child behavior checklist [30]. The objective of the study was to examine the associations among missed sleep, asthma-related quality of life, and indicators of asthma morbidity in urban children with asthma. Given the importance of anxiety as a trigger for asthma symptoms and the link between anxiety and disrupted sleep, the associations among anxiety, asthma morbidity indicators, and missed sleep were also tested. Children with higher anxiety had stronger associations between missed sleep and asthma morbidity such as sports limitations and school absences [30]. As anxiety has been previously described as a trigger for asthma [31], it is therefore possible that nocturnal asthma worsening may disrupt sleep. Anxious children may also have more difficulty returning to sleep due to asthma-specific anxiety and general worries. Hence, family-based interventions focusing on the relationship between anxiety and asthma could reduce night waking frequency and duration and overall asthma morbidity in children [32, 33].

The link between asthma and insomnia raises the question of whether treatment of insomnia leads to better asthma control. A study using 3 mg of melatonin vs. placebo for 28 days in subjects with mild to moderate asthma showed that the melatonin treatment group reported significant improvement in sleep quality as compared to the placebo group at the end of 4 weeks. Interestingly, there were no differences in asthma symptoms, medication use, or PEFR between the two groups [34]. However other studies suggest melatonin in asthma might be pro-inflammatory [35]. Further studies are needed to assess the long-term effects of melatonin and other sleep inductors in patients with asthma.

Sleep-Disordered Breathing and Asthma

SDB is a frequent asthma comorbidity. SDB has a broad clinical presentation, ranging from primary snoring to obstructive sleep apnea syndrome (OSAS) that is considered the most severe entity within the spectrum [36]. SDB has been shown to contribute to neurobehavioral and cognitive morbidity in children, including poor school performance, impaired language skills, attention deficits, hyperactivity, and reduced quality of life [37]. A recent systematic review investigating the association between asthma and SDB showed that SDB was significantly more frequent in children with asthma compared to non-asthmatics (23.9% vs. 16.7%, respectively, $p < 0.0001$) and that children with asthma had a significantly higher risk for SDB with an odds ratio of 1.91 [38]. Moreover, this increased risk of OSAS in asthmatic patients has been reported to correlate with poor asthma control and the need for high doses of inhaled or systemic corticosteroids [39]. There are several plausible explanations for this bidirectional relationship between SDB and asthma. For example, patients with SDB may develop worsening of their nocturnal asthma due to a reflex bronchoconstriction mediated by upper airway vibration and intermittent hypoxemia triggered by partial or complete upper airway obstruction. GERD can coexist with SDB and may also cause reflex bronchoconstriction [25]. This is supported by the "one-airway hypothesis" that suggests that upper airway pathology may influence the course of lower airway disease and vice versa [40]. However, it appears that the asthma-OSAS relationship is bidirectional. Asthma may contribute to OSAS by the following proposed mechanisms: (1) Oxygen free radicals released by the asthmatic airway upregulate the production of cysteinyl leukotrienes, which then induce a proliferative response in the lymphoid tissue, and thus may lead to adenotonsillar hypertrophy [41, 42] (2) Another explanation may involve an infectious agent that can modify the tissue properties across the airways. Specifically, respiratory syncytial virus (RSV) can induce neuroimmune modulatory mechanisms in the lower respiratory tract mediated by neutrophils and leukotrienes, thus maintaining airway inflammation [43]. Since pharyngeal lymphoid tissue is the primary site for the proliferation of respiratory viruses, the increased expression of neutrophils and cysteinyl leukotrienes may result in adenotonsillar hypertrophy [40, 44], which is a mediator for the development of SDB [45].

The link between OSAS and asthma raises the question of whether treatment of OSAS leads to better asthma control. Children are well suited to perform such studies as they are typically treated with adenotonsillectomy (AT), a one-time procedure that does not require adherence. In a study of 25 subjects with asthma, 60% of children were able to eliminate all of their asthma therapies, and 28% were able to eliminate some of their therapies after AT [46]. A single cohort study of children with poorly controlled asthma showed that AT reduced the frequency of asthma exacerbations and bronchodilator usage and led to improvement in the lung function of children with polysomnographic evidence of OSAS [47]. In a large study using the 2003–2010 MarketScan database, AT proved to be beneficial in children with asthma, as their acute exacerbations were reduced by 30.2%, compared to a relative 2%

reduction in children with asthma who did not undergo surgery [48]. Children who underwent AT also had significantly fewer emergency department visits, asthma-related hospitalizations, and bronchodilator or corticosteroid usage [48].

Obesity, Sleep Duration, and Asthma

Obesity is more prevalent in asthmatics [49]. Six hundred and eleven adults at tertiary clinics were surveyed on asthma symptoms and habitual sleep duration. Medical records were used to assess asthma severity step [1–4], extract height and weight, and be informed on current medications and diagnosed comorbid conditions. Forty-one percent of patients were obese. Obesity was associated with shorter and very long sleep duration, highest asthma severity step, and psychopathology including depression, anxiety, panic, and bipolar disorder [50]. Interestingly, obesity was significantly related to highest asthma step following a dose-response pattern, suggesting that asthmatics with poorer disease control may be more predisposed to weight gain and obesity [50]. The mechanisms linking asthma and inflammatory processes with neuroendocrine processes remain unknown. However, leptin may play a role. Leptin is a hormone that also acts as a cytokine in inflammatory/immune responses [51]. Circulating leptin levels are elevated in both asthmatic children and adults, independently of body fat measurements. This may create a state of "leptin resistance" and thus interfere with its role as a regulator of appetite and energy homeostasis favoring obesity in certain patients [52]. It has also been previously suggested that pharmacological asthma treatment and in particular systemic corticosteroids and even inhaled corticosteroids through their systemic absorption may lead to weight increase [53].

Sleep duration is emerging as a risk factor for obesity in population-based studies [54, 55]. In a prospective cohort of young adults, there was a negative association between sleep duration and obesity [54]. Furthermore, short sleep duration appears to be independently associated with weight gain, particularly in young subjects [56]. Asthmatics have also been shown to have a shorter and more disrupted sleep pattern than normal individuals [21]. The data are intriguing enough to warrant further prospective studies to better understand the relationship between asthma and its treatment, sleep, and obesity.

Conclusion

Nocturnal asthma may lead to poor sleep quality, while sleep deprivation may lead to negative asthma outcomes pointing into a bidirectional relationship. On the other hand, asthma often coexists with GERD and SDB, and although a causal relationship has not been established, early identification and management of these conditions may improve quality of sleep and therefore daytime functioning.

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Obesity, Asthma, and Sleep-Related Breathing Disorders

13

Maria Teresa Coutinho and Daphne Koinis Mitchell

Obesity, defined as a body mass index (BMI) of 25 kg/m^2 or more for adults and children, continues to rise in prevalence globally and in the USA and is associated with significant detrimental effects on development and health [1]. Among the US population, prevalence rates between 2011 and 2014 are reported to be 17% in children and 36% in adults [2]. Additionally, there are ethnic and racial, socioeconomic, and residential disparities in obesity prevalence rates within the adult and child populations [2]. Specifically, in the USA, almost half of African American adults are obese (48%), while in children, African Americans (19.5%) and Latinos (21.9%) experience the highest rates of obesity when compared to non-Latino White and Asian children [2]. Higher rates of obesity are also observed in individuals who reside in urban and low-income environments [3, 4]. Obesity is associated with several chronic health conditions, such as cardiovascular disease [5, 6] and diabetes [7]. Obesity is also highly comorbid in individuals who have asthma [8–10] and sleep-related breathing disorders (e.g., obstructive sleep apnea [11–14]). In fact, obesity, asthma, and sleep-related breathing disorders can co-occur frequently, as each condition shares common pathophysiological features (e.g., inflammation), and similar contextual factors (e.g., urban stressors) can exacerbate these conditions. While the treatment approaches for each condition may be unique, together, these comorbidities can have important consequences for an individual's overall health and daily functioning [15–17].

M. T. Coutinho (✉)
Child and Family Psychiatry & Pediatrics, Brown Medical School, Bradley/Hasbro Children's Research Center, Providence, RI, USA
e-mail: mcoutinho@Lifespan.org

D. K. Mitchell
Child and Family Psychiatry & Pediatrics, Brown Medical School, Bradley/Hasbro Children's Research Center, Warren Alpert Medical School of Brown University, Providence, RI, USA

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In this chapter, we will provide a summary of how obesity, asthma, and sleep-related breathing disorders (SRBD) are highly comorbid conditions in both adult and child populations. We describe pathophysiological mechanisms that underlie the association between these conditions, as well as contextual factors (e.g., urban stressors, overcrowding, lack of safe spaces to exercise) that may increase their prevalence and negative impact on health outcomes. Given disparities in the prevalence of obesity, asthma, and SRBD [9, 18, 19], our review considers multilevel factors that contribute to these disparities, as well as considerations for future research, intervention development, and clinical practice for individuals who present with these co-occurring conditions. We discuss the implications of obesity for asthma and SRBD diagnoses and the role of weight management strategies in the treatment of asthma and SRBD. Lastly, we provide recommendations for future research to further understanding of the impact of these co-occurring conditions on health and daily functioning.

Obesity and Asthma

Obesity and asthma are highly comorbid conditions and are disproportionally observed in individuals from ethnic minority, urban, as well as low-income backgrounds [13, 20, 21]. Asthma prevalence has been found to be higher among adults with obesity (11.1%) compared with adults in normal weight (7.1%) and overweight (7.8%) categories [22]. Additionally, asthma prevalence rates differ by gender and obesity status, with no significant differences in rates of prevalence by weight status for men, while women with obesity have higher current asthma prevalence (14.6%) compared to women with normal weight (7.9%) and overweight (9.1%) [22].

A body of research has focused on risk for obesity in those with asthma. Obesity risk has been shown to increase due to a number of factors including challenges engaging in physical activity due to asthma symptoms and/or deconditioning in individuals with asthma [21, 23] Others show that overweight and obese children without underlying lung disease are more likely to present with reduced lung volume measurements [24]. Another set of studies has shown that obesity is a risk factor for asthma diagnoses [17, 21] and has been associated with more severe asthma and poor asthma control [10, 20]. In fact, some longitudinal studies have shown that in obese individuals, the risk for developing asthma was higher than in nonobese individuals [17, 25]. For example, prospective studies of risk factors for children's respiratory health, with children who were free of asthma at study entry, found that children who were overweight (1.52, 95% CI 1.14–2.03) and obese (1.60, 95% CI 1.08–2.34) had a higher risk for later asthma diagnoses [17]. Similarly, other findings indicate that boys with a BMI equal or greater than the 85th percentile were at higher risk for the development of asthma [26]. In summary, asthma and obesity are highly co-occurring conditions. Moreover, it is important to consider underlying mechanisms that contribute to morbidity associated with each condition to improve the assessment and treatment approaches for individuals who have both conditions.

Obesity and Sleep-Related Breathing Disorders

Obesity and sleep-related breathing disorders are highly comorbid in both adult and child populations [11–14]. Significant percentages of individuals with obstructive sleep apnea are found to be obese, and the onset of sleep apnea has been shown to frequently follow a marked increase in body weight [11]. Furthermore, findings indicate that sleep-related breathing disorders are more common within racial and ethnic minority groups [27] and in urban areas [28]. Sleep-related breathing disorders (e.g., obstructive sleep apnea, obesity hypoventilation syndrome) refer to the occurrence of repetitive episodes of complete or partial obstruction of the upper airway resulting in arousals, sleep fragmentation, and intermittent hypoxemia [13]. Sleep-related breathing disorders can affect cognitive and daily function in children and adults alike [15, 29–31]. Sleep-related breathing disorders are associated with poor academic performance [29], poor sustained attention [15, 32], and poor behavioral functioning (e.g., hyperactivity, aggression, poor communication, poor social competence [31]).

Taken together, obesity, asthma, and SRBD are highly comorbid conditions that can each negatively impact an individuals' overall health and daily functioning. Given increases in the prevalence rates of obesity, asthma, and SRBD; their disproportionate burden for low-income, urban, and ethnic minority populations; and their potential cumulative effect on health outcomes and daily functioning, it is important that research and clinical practice consider the significant overlap between these conditions, to inform the development of integrated treatments that can address each condition.

Pathophysiological Mechanisms Linking Obesity and Asthma

There are genetic, mechanical, immunological, and behavioral factors that contribute to obesity and asthma link [33, 34]. These results have informed the concept of two separate obese asthma phenotypes, an earlier-onset allergic disease phenotype and a later-onset non-allergic phenotype, more common in women [33, 34].

Genetics

Research has focused on shared genetic origins between obesity and asthma [33, 35]. Several promising genes connected with both obesity and asthma (e.g., 5q23-32, 6p21-23, 11q13, and 12q13-24) have been identified [33]. Some research focusing on asthma and obesity has shed light on which condition precedes the other [34, 35]. More recently, the work of Ahangari and colleagues [35] suggested a shared genetic pathway for both allergic airway disease and visceral adiposity. Their work provides evidence that chitinase 3-like 1 (Chi3l1), a gene associated with Th2 responses, airway inflammation, and methacholine hyperresponsiveness, is associated with visceral obesity. Additionally, their work provides evidence for the

possibility that a high-fat diet may contribute to increased visceral adiposity and asthma risk by stimulating the Chi3l1 pathway. Additional research is needed to elucidate the role of genetics in mechanisms underlying asthma and obesity and to understand shared mechanisms.

Mechanistic Pathways

There are common mechanistic pathways that link obesity with asthma. Specifically, obesity affects lung function via thoracic restriction and respiratory muscle weakness [23]. Increased BMI has been associated with reduction of forced expiratory volume in one second (FEV1), forced vital capacity, total lung capacity, functional residual capacity, and expiratory reserve volume [23]. Thoracic restriction associated with obesity is usually mild, and attributed to mechanical effects of fatty tissue on the diaphragm and chest wall, such that diaphragm excursion is impeded and thoracic compliance reduced [23]. However, these effects are only clinically significant for those with severe obesity [23, 33]. Additionally, given respiratory muscle weakness, exercise capacity is compromised in severely obese individuals [23].

Inflammatory Processes

Inflammatory mediators are important to consider in both obesity and asthma [8]. Obesity is characterized by increases in the serum concentrations of cytokines, chemokines, acute phase proteins, and energy-regulating hormones including leptin. These mediators are produced by adipocytes and in general called adipokines. Although the precise mechanisms need to be determined, adipokines may alter T helper 1 (Th1) and T helper 2 (Th2) balance, immune tolerance, lung development, airway smooth muscle and airway responsiveness, which are associated with asthma [36]. Increased leptin secretion in obesity may be specifically involved in the development of asthma by modulating airway inflammation [36]. Obesity-related systemic inflammation primes the lung for an exaggerated response to environmental triggers leading to asthma-like symptoms [33, 36]. Genetic, mechanistic and inflammatory processes are important in understanding the high comorbidity of asthma and obesity. Additionally, several contextual factors contribute to increased risk for obesity and asthma and may provide opportunities for tailored interventions.

Contextual Correlates Common to Obesity and Asthma

Contextual factors, specifically nutrition and diet, physical activity, as well as urban stressors, contribute to increased risk for asthma and obesity. Findings document the impact of neighborhood stressors on asthma [37] and obesity [38]. For individuals with asthma living in urban environments, finding safe spaces to participate in physical activity can be difficult; similarly the lack of available low-calorie

nutrient-rich foods in some urban settings (e.g., food deserts) contributes to inadequate diets that are a factor in obesity and poor asthma control [38, 39]. Obese individuals may be deconditioned as well [23]. Developing integrated treatment strategies that address not only individual factors that contribute to poor treatment compliance but also contextual factors that can serve to deter engagement in effective treatment is important to consider when addressing complex comorbid conditions such as asthma and obesity.

Pathophysiological Mechanisms Linking Obesity and Sleep-Related Breathing Disorders

The presence of adeno-tonsillar hypertrophy, which is influenced by inflammatory processes, in addition to functional factors, including increased airway collapsibility and chest wall mechanic alterations present in obese individuals, contributes to greater incidence of SRBD in this population [40]. Excessive weight affects breathing in a number of ways, including alterations in upper airway function and structure, reduced chest wall compliance, and disturbance of the relationship between respiratory drive and load compensation [41]. Recent literature also suggests shared inflammatory processes (e.g., pro-inflammatory cytokines) play a role in obesity and SRBD. Leptin has been associated with inflammatory processes related to the pathogenesis of obesity and SRBD [24].

Comorbidity and Challenges for Diagnoses

Overlapping conditions present a challenge to diagnosis and treatment for individuals and their providers. For individuals with comorbid obesity, asthma, and SRBD, perceptions of symptoms complicate the diagnostic process. For example, perception of dyspnea is often increased in obesity, and an asthma diagnoses may be erroneously made when objective lung function and airway reversibility data is not available [23]. Polysomnography is the gold standard for an SRBD diagnoses, but involves a great deal of resources, which may not be accessible to individuals from low-income populations, and may contribute to undiagnosed SRBD [18]. These challenges are significant and developing cost-effective, easily accessible, objective measures of lung function, and sleep-related breathing would support more accurate and immediate diagnoses, as well as identification of primary targets of intervention, while also recognizing the need for integrated treatment approaches.

Treatment of Obesity, Asthma, and SRDB

For each of these conditions, specific treatment recommendations are available; however, they do not fully consider the co-occurrence of these conditions and the manner in which their comorbidity may affect treatment compliance and response.

We briefly review general treatment recommendations for obesity, asthma, and SRBD. Given our focus on the linkage between obesity, asthma, and SRDB, we discuss in detail the role of weight loss intervention in the treatment of asthma and SRDB while recognizing that it is a challenging intervention to implement successfully. Lastly, we outline suggestions for further research that supports integrated treatment approaches that will contribute to improved health and daily functioning of individuals.

In addressing obesity, the most efficacious interventions include comprehensive approaches that address nutrition, physical activity, and behavioral modifications [42]. These approaches include reduced caloric intake, increasing physical activity, and self-monitoring strategies that support long-term compliance and weight loss maintenance [42]. For asthma, the NHLBI guidelines [43] provide a comprehensive guide for the management of asthma that includes rescue and long-term controller medication (if appropriate), as well as management of environmental triggers. The standard care for sleep-related breathing disorders such as OSA includes the use of constant positive airway pressure (CPAP), but this does not consider weight loss as an adjunct therapy to address sleep issues [24]. Each of these sets of recommendations, while addressing the primary symptoms within each condition, do not fully address their comorbid manifestation. As the recommended strategy for treatment of obesity is weight loss, below we review the literature on the impact of different weight loss interventions on asthma and SRBD, as weight loss may be an important adjunctive component in the treatment of asthma and SRBD.

Role of Weight Management Strategies in the Treatment of Asthma

Effects of Weight Loss on Lung Function

While the NHLBI guidelines recommend participation in physical activity when asthma is in good control, and weight loss when obesity is present, they do not recommend specific approaches for managing asthma when obesity is present [43]. In children and adults with asthma, weight loss has been associated with decrease in asthma symptom reporting, decreased rescue medication use, and improved quality of life [10]. Weight loss resulting from surgery has been associated with improved lung volumes (FEV1 and FVC) with no change in airflow obstruction and reduced airway reactivity in patients with normal IgE [10]. Studies on calorie restriction have documented improved objective markers of airway stability and airflow obstruction, as well as asthma symptoms, rescue medication use, and risk for asthma exacerbation [33].

Some studies have documented impact of weight loss on inflammatory processes for children with associated improvements in asthma control and lung function. In children, weight loss was associated with a decrease in post exercise, decline in lung function, and improved asthma-related quality of life [44]. Studies also indicate that

weight loss has been associated with a reduction in c-reactive protein (CRP) and leptin and exhaled nitric oxide (eNO) [8, 44].

Diet needs to also be considered in the treatment of asthma, and further study is needed to better understand the impact of diet on asthma, specifically on inflammatory processes related to airway constriction. Encouraging patients to maintain a diet that is rich in antioxidants, such as vitamins A, C, and E and selenium [10], may be helpful to support asthma control. Vitamin D supplementation has been shown to be important as an adjunct for persistent asthma treatment, given its role in reducing virally induced airway inflammation, and to improve response to steroid therapy [10]. However, the largest clinical trial of vitamin D3 to decrease asthma exacerbation failed [45]. The literature also suggests that omega-3 polyunsaturated fatty acid intake is inversely associated with asthma [46], and consuming a high-fat meal has been associated with increased airway inflammation and impaired bronchodilator recovery in young adults with asthma [39]. Additionally, omega-3 supplementation has been associated with decreased exercise-induced asthma symptoms [47]. Diets high in omega-3 PUFA and low saturated fat content may contribute to better asthma control; however, the association between low saturated fat, antioxidant-rich diets, and asthma needs to be more adequately studied to better understand the mechanisms underlying those associations.

The use of psychopharmacology interventions to address obesity and the impact on asthma has not been very widely studied. Of significance to patients with asthma is metformin, a drug that is prescribed to patients with obesity and type 2 diabetes mellitus [10]. In addition to weight loss, metformin has the potential to reduce inflammatory processes related to pulmonary health including lipopolysaccharide-triggered airway inflammation [10, 48]. It has not been studied with patients with asthma; however, given its potential effects on lung function, it warrants further study.

Additionally, given health disparities in obesity and asthma, as well as SRBD, treatment recommendations need to consider multilevel risk factors that contribute to higher prevalence rates in low-income, urban, and ethnic minority communities [38, 49]. Interventions considering contextual factors that support and hinder treatment of these comorbid conditions will be important in addressing and mitigating racial, socioeconomic, and residential disparities in obesity, asthma, and SRBD. Interventions that incorporate cultural norms and values related to diet, physical activity, and family involvement are important to consider in addressing obesity, asthma, and SRBD [38]. For example, the availability of community resources has been found to be positively associated with youth's engagement in physical activity [50]. Similarly, in the treatment of SRBD when considering adjunct therapies that address weight loss, identifying factors such as lack of availability of nutrient-rich foods in certain neighborhoods can be an important step in developing targeted and effective treatments. A current intervention with the aim to enhance sleep and asthma symptoms in an urban high school student population integrates sociocultural aspects relevant to sleep hygiene behaviors and asthma management within an urban context [51].

Role of Weight Management in the Treatment of Sleep-Related Breathing Disorders

While studies indicate that surgical weight loss has positive effects for sleep quality and disordered breathing, there is not a complete understanding of the long-term effects of this mode of treatment, and the mechanisms that support these effects are not well understood [52]. Similarly, studies examining the role of dietary weight loss indicate positive effects. Questions remain about what is the ideal amount of weight loss to achieve and maintain improvement in sleep-disordered breathing and how to support maintenance of weight loss beyond 6–12 months [52]. Lastly, further study is needed to fully understand the effects of weight loss on upper airway functional and structural changes [24].

Recommendations for Future Research

The literature identifies clear linkages between obesity, asthma, and sleep-related breathing disorders. However, further research is needed to elucidate the underlying genetic, biological, and behavioral mechanisms that support these associations. Additionally, a better understanding of integrated treatment approaches that prioritize symptoms and reduce burden is important to support individuals' improved overall health and functioning.

Genetics and Pathophysiology

Promising findings indicate shared genetic pathways for the development of asthma and obesity; extending this work to evaluate common genetic pathways in SRBD may support the development of interventions targeting specific mechanisms of action. Further research is needed regarding the pathophysiological mechanisms (e.g., inflammatory mediators) that might interact to directly affect asthma and SRBD in the presence of obesity. There is a need for prospective studies examining the co-occurrence of asthma symptoms, obesity, and sleep-related breathing disorders to better understand the causal relationship between obesity, asthma, and sleep-disordered breathing.

Behavioral/Contextual Factors

Additional study is needed to understand the consequences of co-occurring obesity, asthma, and sleep-disordered breathing in areas of functioning beyond quality of life, for example, academic functioning, concentration and attention, work productivity, and emotional functioning. The use of objective measures to assess lung function and sleep-related breathing would support a clearer understanding of these associations. Clarifying the use of general measures of obesity (e.g., BMI) in comparison to measures such as dual energy x-ray absorptiometry-measured mass (DEXA) which allows for more accurate quantification of body fat and its

distribution would also support a better understanding of the role of obesity in asthma and sleep-related breathing processes [53]. Given cultural norms and values associated with diet, sleep, and understanding of disease processes, such as asthma, it is important for intervention development research to examine and consider culturally tailored approaches that address these issues [9, 38].

Integrated Treatment Approaches

Given high rates of comorbid obesity, asthma, and SRBD, the development of integrated treatment approaches is of paramount importance for improving individuals' health. Approaches that assess the existence of comorbid conditions at diagnoses, and facilitate the development of a tiered treatment approach, targeting symptoms according to level of risk are important to consider. Providers need to work collaboratively with individuals to assess the illness-specific factors that contribute most to decreased quality of life and daily functioning and develop individualized approaches to treatment. Additionally, the use of interdisciplinary team approaches that minimize patient burden (e.g., appointments in different clinics with different providers) while maximizing expertise that supports treatment adherence is important to consider. For example, for asthma and obesity, the addition of behavioral experts (e.g., psychologists) who can work with patients to address and develop behavioral plans that support medication adherence and barriers to physical activity would enhance treatment. Similarly, educating patients in a systematic and supportive fashion about each condition and their specific and combined effects on aspects of physical and daily functioning may enhance individuals' treatment compliance. Lastly, acknowledging individual's cultural values (e.g., medication beliefs) and aspects of their environment (e.g., lack of spaces to exercise, shared sleeping quarters) that may impact treatment and developing strategies that address these issues are important for effective disease management.

In summary, obesity, asthma, and sleep-related breathing disorders are highly comorbid, and prevalence rates continue to rise, contributing to alarming negative effects for individuals' health and well-being. Additionally, these conditions present a disproportionate burden for ethnic minority, low-income, and urban populations. Current data supports a growing understanding of common genetic, pathophysiological, and contextual factors that contribute to the risk for developing obesity, asthma, and SRBD. Further research is needed to understand these underlying mechanisms and to develop integrated treatment strategies that prioritize targets of intervention according to level of risk.

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Monitoring Asthma During Sleep: Methods and Techniques

14

Katalina Bertran, Trinidad Sánchez, and Pablo E. Brockmann

Associations between allergic sensitization and asthma morbidity in children have been demonstrated frequently in the literature [1, 2]. Sleep is a major issue to evaluate when considering asthma patients. Shortcomings of self-reported assessments suggest a need for objective measure in many patients.

Airway inflammation results from the activation of mast cells and antigen-specific type 2 T-helper cells (Th2 cells) and results in cytokines, including interleukins (IL-4, IL-5, and IL-13). These cause the upregulation of epithelial inducible nitric oxide synthase (iNOS) expression and the consequent increase in NO generation [3].

Subjects with wheezing are at risk for sleep disturbance and secondary daytime cognitive dysfunction. Asthmatic children have more frequent snoring, apneas, and hypopneas during sleep than non-asthmatic subjects, and tonsillar hypertrophy mediates at least in part this epidemiologic association. Also preliminary evidence indicates that treatment of sleep apnea with adenotonsillectomy results in improved control of coexisting asthma [4]. Elevated concentrations of leukotrienes and oxidative stress markers have been detected in the exhaled breath condensate of children with asthma, probably contributing to bronchoconstriction. Besides children with obstructive sleep apneas show an increased expression of leukotrienes and leukotriene receptors in adenotonsillar tissue. Therefore, there seems to be an epidemiologic connection between SDB and asthma [5, 6].

K. Bertran · T. Sánchez · P. E. Brockmann (✉)
Department of Pediatric Cardiology and Pulmonology, Division of Pediatrics and Sleep Medicine Center, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile
e-mail: pbrockmann@med.puc.cl

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The prevalence of sleep, disturbed by wheezing and coughing, has been reported in 38.95% of asthmatic children [7]. Nocturnal symptoms are a sign of poor asthma control and are associated with worse clinical outcomes in children and adults [8]. Furthermore, poor asthma control is predictive of more sleep problems in children [9].

Monitoring asthma during sleep is challenging because standard asthma evaluation requires the patient to be awake and to cooperate. However, several techniques have been developed and will be addressed in this chapter.

Methods and Techniques

Fe(NO) and n(NO)

The analysis of fractional exhaled (Fe)NO and nasal (n)NO adds an objective, rapid, and cost-effective method for monitoring airway inflammation, helping in the management of obstructive sleep apnea syndrome (OSA) (Table 14.1) [10, 11].

Repetitive airway closing and opening during apnea episodes and nonspecific mucosal epithelial cell hyperactivity of hypertrophic adenoids and tonsils cause upregulation of inflammatory cytokine expression and increased NO generation. Also intermittent hypoxia is in part responsible for airway inflammation and the generation of reactive oxygen species [12]. The abovementioned studies focused on adults, and evidence on children is scarce.

Huang et al. demonstrate differences in (n)NO and (Fe)NO concentration in children with SDB with nocturnal symptoms and OSA (AHI > 1/hour) versus controls. Their results included a (n)NO in parts per billion (ppb) of 111.0 (544.0;349.0) and (Fe)NO concentration of 12.0 (9.8;14.0) (ppb). Compared to healthy children, (n)NO concentration correlates with apnea-hypopnea index (AHI; $r = 0.429$, $p = 0.018$) and inversely correlates with oxygen saturation (SaO2; $r = -0.482$, $p = 0.007$) [3].

Table 14.1 Methods and techniques for monitoring asthma during sleep

1.1 Fe(NO) and n(NO)
1.2 IOS (impulse oscillometry)
1.3 Noise measurement in sleep: objective cough monitoring system; mobile recording and analyzing system (LEOsound); tracheal sounds; snore; and SpO_2 measurement (SNORESAT)
1.4 Sleep diaries
1.5 Chest wall electromyography
1.6 Wireless portable systems
1.7 Actigraphy

IOS (Impulse Oscillometry)

Although not routinely used during PSG, impulse oscillometry (IOS) is a computer-supported method for the measurement of small and large airway resistance that is performed in children too young to perform standard pulmonary function testing. In this method, pressure fluctuations are applied on the airway of the patient's normal, quiet, tidal breathing. It's highly suitable in pediatric patients, noninvasive, and minimally dependent on patient's cooperation.

During sleep, there is a physiological decrease of muscular tone in the upper and lower airway that changes during different sleep stages. In asthmatic patients, due to lower airway constriction, they may experience wheezing and arousals due to respiratory symptoms. This results in fragmented, non-restorative sleep. This non-restorative sleep predisposes to neurocognitive, cardiovascular, and metabolic consequences, especially in children. Due to the impact of upper and lower airway resistance during sleep, it is important to monitor this if possible in these patients.

IOS has been tested to evaluate clinical outcomes in chronic obstructive pulmonary disease (COPD) and asthma in adults and children [13, 14].

The association between adenotonsillar hypertrophy and allergic rhinitis in sleep breathing disorders often causes nasal mucosal swelling, increasing the risk of OSA in children and increasing upper airway resistance. Nevertheless, the association between airway resistance and OSA in children remains a matter of controversy.

Zhang et al. [15] compared children diagnosed with OSA versus primary snorers measuring total airway resistance (R5), proximal resistance (R20), and peripheral airway resistance (X5) with IOS. Total airway resistance in the OSA group was significantly higher than that in the non-OSA group ($p = 0.0025$). Also total airway resistance was positively correlated with apnea-hypopnea index and obstructive apnea index and negatively correlated with the lowest arterial oxygen saturation ($p < 0.05$).

Campana et al. [8] developed an invasive IOS, a forced oscillation system (FOT) used during sleep to characterize mechanical properties of upper and lower airway resistance. It consisted of an epiglottic catheter that recorded oscillations in Hz during the entire night. It was well tolerated in three adults (healthy, asthmatic, and with OSA) with and without positive airway pressure. The system was able to calculate resistance accurately in all described subjects, monitor changes during breathing cycles, detect changes in caliber of the upper airway in OSA patients, and determine when there was collapse.

Noise Measurement in Sleep

Pediatric patients with asthma and respiratory symptoms, such as cough and wheezing, are frequently associated with acute exacerbation in asthma. Many patients report persistent cough during sleep. Studies on coughing have mainly been dependent on subjective reporting. These methods tend to be imprecise and influenced by

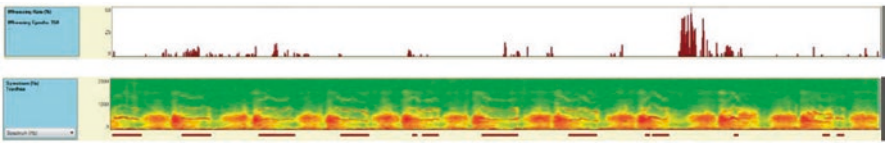


Fig. 14.1 Nocturnal wheezing recorder by LEOsound. Nocturnal wheezing events displayed in red. Spectrogram showing wheezing on the basis of characteristic frequency curve. (From Koehler et al. [17], with permission.)

many factors, including environment, clinical setting, and even personality of parents. They also do not necessarily reflect nocturnal symptoms.

Although several devices are available/in development to this, Hirai et al. [16] published an objective cough monitoring system that specialized in children, measuring cough frequency and nocturnal cough patterns. Coughs were recorded with microphone and accelerometer, using a customized software program. A number of nocturnal coughs and pattern of cough frequency in 30-minute intervals were measured along with the severity of each asthma exacerbation. Total overnight cough count in children with asthma was higher than in controls ($p < 0.001$). Also total overnight cough count was significantly higher in severe asthma attacks versus moderate ones ($p < 0.05$), and cough counts were increased at falling asleep and waking.

Koehler et al. [17] developed a mobile recording and analyzing system (LEOsound) for sleep respiratory symptoms in asthmatic children. Through a spectral analysis of respiratory noises, the instrument can separate wheezing from coughing (Fig. 14.1). This objective monitoring promises improvement in asthma diagnosis and management.

An interesting study performed in adults measured tracheal sounds and a simultaneous polysomnography. Tracheal sounds were digitized and recorded as power spectra. An automated computer program detected transient falls (TS-dip) of sound, calculating a moving average of the logarithmic power of tracheal sound. Nakano et al. defined the tracheal sound-respiratory disturbance index (TS-RDI) as the number of TS-dips per hour of examination. Oxygen desaturation index was also calculated based on the TS-dip (SpO_2 dips of 4% from baseline). The TS-RDI highly correlated with Apnea-Hypopnea Index (AHI) ($r = 0.93$). Mean (±SD) difference between the TS-RDI and AHI was -8.4 ± 10.4. Agreement of TS-RDI and AHI was better than SpO_2 desaturation index and AHI. Nakano et al. concluded that fully automated tracheal sound analysis demonstrated a relatively high performance in the diagnosis of sleep apnea-hypopnea syndrome, showing this method to be useful in portable monitoring of sleep apnea-hypopnea syndrome (Fig. 14.2) [18].

In another study conducted by Issa et al. [19] performed in adults, a new portable digital recorder system (SNORESAT) was used that uses the sound of snoring and arterial oxygen saturation (SpO_2) to monitor breathing abnormalities during sleep polysomnography (PSG). This device digitally recorded sound from a transducer applied to the chest and SpO_2 from a commercially available ear oximeter. A snore was identified when the sound exceeded a threshold voltage level longer than 0.26 seconds. An analysis algorithm identified a respiratory disturbance event when a quiet



Fig. 14.2 Tracheal sound analysis. (From Nakano et al. [18], with permission.)

period of 10–120 seconds separated two snores and were associated with a fall in SpO_2 of 3%. Using the computed RDI recorded by the SNORESAT, the sensitivity and specificity of the monitor in detecting sleep apnea-hypopnea syndrome (OSA) depended on RDI range (≥10 or ≥ 20 RD/hour) and ranged from 84 to 90% and 95 to 98%, respectively. A positive diagnostic value from the SNORESAT increased the probability of OSA to 95–96%, whereas a negative value from the SNORESAT decreased the posttest probability of OSA to 4–12%. Issa et al. concluded that laboratory testing of SNORESAT can estimate the presence or absence of nocturnal breathing abnormalities with adequate accuracy and is clinically useful in diagnosing OSA.

Sleep Diaries

Sleep and asthma questionnaires are low cost, easy to apply, and available instruments used for clinical and research purposes. There are several sleep diaries that can be used in healthy or chronic children to monitor sleep quality and symptoms, based on subjective parental report. As described before, nocturnal asthma symptoms or awakenings are indicators of poorly controlled asthma. Yoshihara et al. [20] developed a short nighttime sleep diary in children from 6 months to 6 years, based mainly in nighttime awakenings frequency and daily use of asthma medication (Fig. 14.3). The nighttime sleep diary was compared to the traditional asthma diary, which included exacerbations, wheezing, chest tightness, coughing, and daily use of asthma medications. The nighttime awakening score correlated with both daytime asthma symptom score ($r = 0.663$, $p < 0.001$) and nighttime asthma symptom score ($r = 0.628$, $p < 0.001$). Also the number of days with nighttime awakening was strongly correlated with the number of days with coughing ($r = 0.747$, $p < 0.001$). Finally, the concordance rate was 79.4% between nighttime awakening and daytime symptoms and 74.5% between nighttime awakening and symptoms. The authors concluded that the nighttime sleep diary was a useful instrument to monitor asthma symptoms in infants and young children with asthma.

Month/date (the day of the week)			/ ( )	/ ( )
Nighttime awakening because of asthma symptoms (check only one)			☐ Never	☐ Never
			☐ Rarely	☐ Rarely
			☐ Frequently	☐ Frequently
			☐ Always	☐ Always
Medication adherence*1	Controller	*3	○ · △ · ×	○ · △ · ×
			○ · △ · ×	○ · △ · ×
			○ · △ · ×	○ · △ · ×
			○ · △ · ×	○ · △ · ×
	Reliever		*4	
	Others		○ · △ · ×	○ · △ · ×
			○ · △ · ×	○ · △ · ×
Doctor visit*2			S · U · E · H	S · U · E · H
Comments				

* 1 ; ○ ; good adherence to prescribed dosage and frequency,
△ ; not good adherence to prescribed dosage and frequency,
× ; medication not taken
* 2 ; S ; Scheduled, U; Unscheduled, E ; ER Visit, H ; Hospitalization
* 3 ; medication name, dosage, frequency
* 4 ; record the number of puffs/tablets

Fig. 14.3 Sleep diary. Nighttime sleep diary including nighttime awakening, medication adherence, and medical visits. (From Yoshihara et al. [20], with permission.)

Chest Wall Electromyography

Given the difficulty in monitoring asthmatic patients throughout the night, there are other techniques of interest that have been developed in the past few years. The neural respiratory drive can be measured by respiratory muscles electromyography in order to evaluate the severity of nocturnal asthma. When a respiratory disease progresses in severity, the activity of diaphragmatic and auxiliary respiratory muscles increases. Specifically, the parasternal intercostal muscles are important extradiaphragmatic inspiratory muscles that are recruited in cases of severe asthma. This occurs because the increased airway resistance produces hyperinflation, alters the chest wall and respiratory muscle organization, and increases neural respiratory drive and finally, the respiratory diaphragmatic and extradiaphragmatic muscle activity. This issue was addressed by Steier et al. [21] who measured nocturnal electrical activity of the parasternal intercostal muscles bilaterally in the second intercostal space using surface electrodes in adults with

controlled and uncontrolled asthma, at the same time as PSG. Neural respiratory drive in wakefulness and when waking up in the morning was elevated in those with uncontrolled asthma. Patients with controlled asthma had mildly elevated levels of parasternal electromyography (EMG) only in the morning compared to controls. This technique had an acceptable coefficient of variation throughout the night comparable between normal and asthmatic subjects.

In children, changes in the clinical asthma score corresponded significantly with changes in amplitude of diaphragmatic and intercostal EMG. Maarsingh et al. [22] recruited a group of 16 infants and toddlers hospitalized with asthma exacerbation and compared referred symptoms with EMG. The correlation coefficients of the combined leads of the intercostal and diaphragm EMG were higher than those of the separate leads. EMG is a technique that accurately identifies uncontrolled or controlled asthma, especially for subjects that are not able to perform lung function tests, such as children and adults asleep. While not commonly used as a clinical diagnostic tool, this mode of measure requires further investigation.

Wireless Portable Systems

Portable monitoring systems have been proposed as a diagnostic alternative for different respiratory diseases. In OSA, for example, polysomnography is the gold standard but is expensive and not available widely. Portable monitoring could offer an interesting alternative. For asthma, spirometers are not easily portable. However, Cao et al. [23] proposed a wireless portable system using a microthermal flow sensor to monitor respiratory airflow, a triaxis microaccelerometer to monitor body posture, and a microphotoelectric sensor to monitor blood oxygen saturation. The data can be delivered through Bluetooth to cellular networks or internet, making telemedicine achievable. This technique can be used in adults and children, because the flow sensor monitors respiratory flow directly and is extremely sensitive to weak airflow, detecting airflow of 0.6 L/minute (for preterm and newborns) or 1.8 L/minute (for infants), with a range of 0–10 L/minute. Therefore, this system could be used as both sleep recorder and spirometer at the same time. While not widely published, there are several other investigations ongoing into less invasive and portable devices to measure both lung function and polysomnography.

Actigraphy

The actigraph is a lightweight wrist or ankle accelerometer that records a digitally integrated measure of gross motor activity and can be used to visualize activity during sleep and wake. In can distinguish sleep from wake using proprietary algorithms that have been validated against PSG. Total sleep time, sleep efficiency, duration of awakenings after sleep onset (WASO), and sleep onset latency can be assessed and

analyzed with specific software. In adults, wrist actigraphy has shown to indirectly measure asthma control as it has been reported that the degree of asthma control correlates strongly with sleep quality. Poorly controlled asthma patients have greater sleep onset latency, less sleep efficiency and number of sleep episodes, and more total time awake [24]. As sleep disturbances are common in asthmatic patients, actigraphy can be an easy ambulatory monitoring tool for sleep quality and asthma control.

Conclusions

Given that nocturnal symptoms of asthma are predictive of disease control, it seems essential to have different methods and techniques of nocturnal respiratory symptoms monitoring. Future directions in this matter will be elucidated as newer technologies become available.

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Asthma Treatment Outcome Measures

15

Manisha Witmans

Asthma and the Burden of Disease

Asthma is defined as a chronic, systemic inflammatory disorder of the airways causing symptoms associated with chronic, widespread variable airflow obstruction that is often reversible, spontaneously or with treatment, and is associated with airway responsiveness to various stimuli [1, 2]. Chronicity affects healthcare utilization, quality of life, and productivity at home and at school and can result in death. The most robust information about the prevalence of asthma comes from the data collected by the International Study of Asthma and Allergies in Childhood (ISAAC) conducted in the 1990s involving 306 centers in 105 countries based on standardized self-reported (or parent-reported) questionnaires [3–5] based on school-aged children 6–7 years and 13–14 years old in specific geographic locations. The reported prevalence rate of asthma ranged from as little as 0.8% to as high as 50% in older children based on the self-reported prevalence of wheeze in the last 12 months [4, 5]. The most recent prevalence of asthma is estimated to be 7% in France and Germany, 11% in Canada, and 15–18% in the United States [6, 7]. When considering the actual treatment of asthma based on medical expenditure, the prevalence rate is estimated to be about 4.8% [8]. The economic burden resulting from asthma is staggering. It is estimated that the healthcare cost of asthma were as high as $82 billion in 2013 [9, 10]. Furthermore, there is an underappreciated burden of disease which includes parents taking time off work, large direct and indirect healthcare costs, productivity losses for all those affected, and reduced quality of life. It is estimated to account for approximately 14.2 million lost work days annually [11] in the United States. In fact, asthma is often cited as one of the top ten causes of

M. Witmans (✉)
Division of Pediatric Pulmonology, Department of Pediatrics, The Stollery Children's Hospital & University of Alberta Hospitals, Edmonton, AB, Canada
e-mail: manisha.witmans@ualberta.ca

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disability-adjusted life years in children and young adults. In adults, it ranks second to chronic obstructive pulmonary disease (COPD).

Asthma is characterized by variable and reversible airflow obstruction resulting in symptoms of cough, wheeze, chest tightness, and shortness of breath. Asthma can develop at any time, ranging from infancy to adulthood. Nevertheless, most asthmatic patients develop symptoms by 3 years of age [12]. Pediatric OSA also can occur at any age. Maturational implications may be more significant if not diagnosed and treated very early in childhood (potentially within the first 3–5 years of life) [13, 14]. In childhood, boys suffer from asthma more than girls. However, by adulthood the gender ratio is reversed, and the mechanisms for this change are not fully understood, but hormones likely play a role. Despite the increased prevalence of OSA in adult males (likely due to increased prevalence of obesity), in pediatric OSA there is not a clear gender predilection [15], except in children less than 2 years of age in which there is a slightly higher risk in boys [16, 17].

The trajectory of asthma suggests that although there might be periods of minimal symptoms during childhood, those with frequent or persistent asthma tend to have lifelong symptoms and disease burden. Asthma is also more common in minority populations.

Asthma is a complex, chronic heterogeneous disease associated with several phenotypes. The etiology is multifactorial with genetic, epigenetic, developmental, and environmental factors playing a role. Similar etiological factors are present for pediatric OSA. Evidence suggests that adversities experienced in childhood can have lifelong consequences and affect the foundations of health [18]. The earliest work supporting this idea was the ACE (Adverse Childhood Experiences) Study which was designed to examine the long-term relationship between adverse childhood experiences and a variety of health behaviors and outcomes in adulthood [19]. They collected information on 17,337 adults in 1995–1997 about childhood exposure to adverse experiences (abuse, emotional, physical, or sexual, witnessing domestic violence, parental separation or divorce, growing up in a household where members are diagnosed with mental illness, substance abuse, or being sent to prison) and their association with disease and health status. They found that childhood adversity (childhood traumatic stressors and smoking) is associated with the risk of lung cancer [20]. Based on a systematic review of the evidence, the authors state that since childhood adversity affects brain development and body systems, the role of childhood adversity should be considered when discussing developmental delay, asthma, recurrent infections, somatic complaints as well as sleep disruption, and even response to asthma treatment [21]! These in turn are associated with alterations of immune and inflammatory response and stress-related downstream regulation. Both may be associated with asthma and pediatric OSA. Prevalence of severe OSA in children with moderate asthma appears to be significantly higher than in those with intermittent and mild asthma [22]. Asthmatic children with OSA complain more of snoring, disturbed sleep, sleep-related diaphoresis, and daytime napping [22]. Too often, in the clinical setting, the focus tends to be on the presenting complaint and symptom treatment without consideration of the factors that may potentiate, propagate, or result in perpetuating the disease burden.

Although there is some understanding of the genetic and environmental interactions, there is a lack of precision at the level of the patient to optimally choose the best treatment options for optimal health and functioning. More extensive longitudinal studies are warranted to understand the epigenetic factors and their interaction with the environment resulting in the phenotypic expression of disease. Without that understanding, guidelines will lack the precision to be effective in optimally treating patients, influence the trajectory and outcomes of chronic disease, and reduce the economic burden of asthma and pediatric OSA.

Pathogenesis of Asthma

Genome-wide association studies of asthma in children and adults have identified an association between polymorphisms for IL33, IL1RL1/IL18R1, HLA-DQ, SMAD3, and IL2RB9 and the locus on chromosome 17q21 including the genes ZPBP2, GSDMB, and ORMDL3 [23, 24]. These genes are associated with abnormalities in the epithelial barrier function and affect the innate and adaptive immune responses which play a role in the development of asthma. There also may be some overlap with inflammation associated with pediatric OSA [25–27]. However, the genetic variants alone cannot determine which individuals will develop the disease nor explain the global variations or transient prevalence rate over time [28, 29]. Two significant risk factors for asthma development include allergic sensitization and respiratory tract infections at an early age. Asthma is typically classified with the presence of (1) eosinophilic or high type 2 airway inflammation (present in about 50% of adults and linked with allergy), (2) non-eosinophilic asthma (neutrophil-predominant asthma), or (3) a combination of both eosinophilic and non-eosinophilic asthma. These might affect both the upper and lower airway. The cellular mechanisms involved in each of the subtypes will influence the type of targeted medical therapy. It could be argued that the inflammation from allergies, obesity, or even sleep deprivation also adds enough systemic inflammatory burdens to explain the rising prevalence. If that is indeed the case, the treatment of asthma should involve more comprehensive multimodal therapy targeted at different aspects that may contribute to the inflammation rather than just symptom control.

Global patterns of migration provide information about the environmental factors which play a role in the development of asthma [30], in that, individuals from areas of low prevalence of asthma have increased risk of asthma as much as those in areas of high prevalence over time. The “Westernization” of lifestyle is implicated in the dramatic rise of asthma prevalence [31]. To summarize, factors that prevent asthma include diverse microbiome, acquired from farm living or potentially from household pets (such as dog). Cat on the other hand is so allergenic; it does not appear to confer a protective benefit for asthma development. Breastfeeding might also help. In contrast, rhinovirus and RSV infections appear to increase risk of

asthma development. Limiting cigarette smoke and allergen exposure in the household, including in utero, might also be of benefit. There are several other environmental factors which likely influence asthma outcomes, and more work on this topic is needed.

Definition and Clinical Presentation of Asthma as It Relates to Sleep

Nocturnal asthma symptoms often present with objective coughing. Patients however can underestimate the frequency of symptoms. A dry, nighttime cough is often the marker for asthma control and is noted in the GINA (Global Initiative for Asthma) guidelines. This nocturnal coughing can result in sleep disruption and thus sleep fragmentation and nocturnal waking. Daytime symptoms of that may include but not be limited to excessive sleepiness, hyperactivity, learning difficulty, attention/concentrations problems, and mood disorders [32]. Mechanistically, increased airway resistance in the form of snoring or noisy breathing or labored breathing should be considered and should raise a flag to consider pediatric OSA. Restless sleep can be seen in both asthma and pediatric OSA. Stigmata of atopic disease (allergic shiners, allergic crease, eczema, etc.) may or may not be present in children who present for assessment of asthma or sleep disordered breathing.

Diagnosis of asthma is recommended to be made clinically, based on typical symptoms which respond to bronchodilation. Intensive methacholine challenge is not considered the gold standard. Pediatric OSA, however, cannot be diagnosed on history and physical findings alone [33]. With regard to asthma, the ability to engage in strenuous play or exercise is important to consider. In children or adults, irritability, mood changes, and tiredness or fatigue when participating in activity may also provide clues about asthma or pediatric OSA. The presence of the snoring or increased airway resistance or restless or non-restorative sleep can also be additional clues.

Treatment of Asthma

The understanding of the pathophysiology involved in asthma has resulted in development of more comprehensive and targeted therapies to lessen asthma burden. The goals of asthma treatment include improving quality of life by decreasing the morbidity related to uncontrolled asthma, decreasing symptoms (day-to-day symptoms, disturbed sleep, and activity limitations), reducing risk of exacerbations, reducing adverse asthma outcomes (persistent airflow obstruction or airway remodeling, medication side effects), and preventing asthma-related deaths [34, 35]. Patient's goals and clinician goals may not match perfectly and should be considered in management. GINA guidelines state that optimal asthma control is defined as the following: (1) absence of daytime symptoms more than twice per week, (2) absence of activity-related symptoms, (3) use of short-acting beta agonist less than two times a week,

and (4) absence of night waking due to asthma. NHLBI guidelines suggest the definition of adequate asthma control depends on age, and in older children and adults rare (~monthly) nighttime symptoms are acceptable. Additional factors that would suggest optimal asthma control in view of allergy- and sleep-related symptoms include the absence of snoring or labored breathing (marker of increased airway resistance) and restorative sleep (absence of restlessness, the patient waking up feeling rested).

Treatment Approaches in Asthma

Treatment approaches for asthma, as with any other chronic disease, involve an individualized personalized approach, which includes self-management education or written action plan, inhaler training, treatment of comorbidities and modifiable risk factors, non-pharmacological treatments (weight loss, removal of environmental risk factors that worsen asthma control), and pharmacological treatment adjusted to each patient's phenotypic profile [36]. Along with the symptom control, other common factors that are risk predictors in adults and children should also be evaluated. There are also some data suggesting that treatment of pediatric OSA results in improvement of frequency and severity of asthma. The exact mechanisms are unclear [37]. Shared decision-making between the patient and the treating clinician results in improved patient-centered outcomes [38].

Other Non-pharmacological Interventions

Evidence supports that asthma is linked with psychological and behavioral factors, much like with sleep disorders. Despite the advances in pharmacology as well as delivery devices, poor asthma control is common in clinical practice [39]. Living with asthma has been linked to depression, anxiety, insomnia, and poor sleep continuity. Those with severe or difficult-to-control asthma have a higher prevalence of psychological comorbidity and greater healthcare utilization [40, 41]. Interventions that are commonly used to treat insomnia such as cognitive behavioral therapy may also be useful for treating asthma. A systematic review [42] evaluated non-pharmacological interventions for adults with asthma. Despite the trial heterogeneity and limited clear guidelines, cognitive behavioral therapy variability (similar to how it is delivered for insomnia) seems to have consistent positive effect on asthma-related quality of life and psychological outcomes [43, 44].

Treatment Outcome Measures

The key goals in the treatment of asthma are to reduce morbidity and mortality and optimize health and well-being. [45]. For many children, the outcome measures used by most clinicians rely on patient history and symptom control based on

observation of parents or caregivers. These secondary reports might underreport asthma symptoms. Conventional outcome measures of asthma control include symptom control, pulmonary function tests, and cellular mediators of inflammation as markers of control of inflammation such as immunoglobulin E, IL-10, or exhaled nitric oxide and quality of life measures. Some of these parameters may not only be useful in diagnosing asthma, but they may also help in evaluating interventions. Additional tools which may also be helpful could be other surrogate markers of health and well-being which include restorative sleep, absence of symptoms of sleep disorders breathing, improved quality of life, and improvement in overall functioning with treatment. Given that asthma management is becoming more formulaic, choice of outcome measures should consider local/regional policy in addition to local community needs.

The type of outcome chosen to best represent the improvement in asthma management depends on the time scale one chooses. Acute effects of medications may be best measured considering day-to-day differences, whereas factors such as growth suppression from use of inhaled steroids would be assessed over a period of a decade. As the science has advanced, there is ongoing interest in using more objective markers of asthma diagnosis and control, such as lung function, and not just symptom control. Since it is known that individuals with asthma and sleep disordered breathing have a hard time falling asleep, more frequent nighttime awakenings, less total time of sleep, and poorer quality of life, optimal asthma control should consider assessment of insomnia.

Patient- and Parent-Reported Outcome Measures

As mentioned above, clinical outcomes of asthma treatment and assessment of asthma control are commonly completed by patient report or parent proxy report in the case of young children. Most commonly in the United States, the Asthma Control Test and Asthma Control Questionnaire are used, but there are several acceptable measures (Table 15.1). In addition to objective pulmonary function testing (such as spirometry), recent exacerbations, and therapy required to maintain control, these measures are used to gauge overall asthma control and determine whether a "step up" or "step down" in treatment is warranted. These measures are also used in clinical trials in addition to very specific assessments of exacerbation/control (such as unscheduled visits to PMD/ED, etc.). Clinical trials and clinical care might also assess asthma impact on quality of life.

As far as impact on quality of life, there are several measures which can provide adequate assessment [46]. The new Patient-Reported Outcomes Measurement Information System (PROMIS) Asthma Impact tool is one such measure that assesses various quality of life domains impacted by asthma, resulting in a simple and easy-to-use normalized T-score [47]. The PROMIS measures can also be assessed in conjunction with other PROMIS measures that can further assess domains that are specifically problematic for a particular patient, such as depression, fatigue, etc.

Table 15.1 Subjective measures of asthma control

	Pros	Cons
Asthma diaries	Do not depend on patient recall	They can be retrospectively filled in
	Monitor asthma-related events in real time	Each diary collects large amounts of data
		Lack of a standardized method to account for outcome data
Asthma symptom questionnaires		
ACQ, ACT, cACT, TRACK	Changes in composite asthma scores correlate to clinical deterioration and the need for step-up therapy	Depend on patient recall
	Provide data easy to analyze	Focus on a small-time window
CASI	Identify differences between patients who could seem similar only on the basis of their clinical symptoms	Need for additional studies to validate the application of this tool
	Useful in clinical research to test impact of additional treatment in the context of standard care	Its role in clinical practice is unclear
		It does not include some relevant aspects of disease control
APGAR	Provides a wider spectrum of information than other questionnaires, about features that can be crucial in therapeutic planning	Need for additional studies to validate the application of this tool in clinical practice or clinical research
	It is linked to a care algorithm, which can help the physician to undertake a therapy	
VAS	Quick and feasible tool for real-life monitoring	Need for additional studies to validate the application of this tool in clinical practice or clinical research
	VAS <6 is a reliable marker of uncontrolled asthma	
	Provides information about symptom perception	

From Licari et al. [48], with permission
ACQ asthma control questionnaire; *ACT* asthma control test; *APGAR* activities, persistent, triGGers, asthma medications, response to therapy; *cACT* childhood asthma control test; *CASI* composite asthma severity index; *TRACK* test for respiratory and asthma control in kids; *VAS* visual analog scale

Conclusions

Asthma is a lifelong chronic condition involving inflammation, and its link to allergy and sleep as well as sleep disordered breathing is becoming increasingly recognized. The etiology of asthma is complex, and when assessing treatment outcomes, the broad range of triggers should be considered. Treatment should be targeted to limit daytime/nighttime impairment from asthma, as well as minimize the risk of exacerbation. Both patient report and objective biomarkers are crucial adjuncts to targeting treatment. Several treatment outcome measures should be used in the clinical setting.

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Guidelines for Management of Sleep-Related Breathing Disorders and Asthma

16

Daniel Cerrone, Emily Gillett, and Sally Ward

Asthma in General

Asthma is a significant source of morbidity, and it is estimated that as many as 300 million individuals suffer from asthma worldwide [1]. The National Asthma Education and Prevention Program's Expert Panel defines asthma as the presence of airway obstruction, inflammation, and hyperresponsiveness, with variable and recurring symptoms [2]. The spectrum of severity is varied, and the terms intermittent and persistent asthma have been developed to capture the heterogeneity in presentation. Intermittent asthma is characterized by infrequent symptoms of cough, wheezing, and nocturnal awakenings. Pulmonary function testing obtained on these patients is often normal and rarely will these patients experience exacerbations. Persistent asthma is associated with worse morbidity, impaired pulmonary function, more frequent exacerbations, and greater strains on healthcare. Persistent asthma is typically treated with inhaled corticosteroids; however, in the setting of suboptimal control, a variety of medications can be added including leukotriene receptor antagonists, long-acting bronchodilators, and novel biologic therapies.

A feature of asthma that is shared by both intermittent and persistent asthma is the asthma exacerbation which is characterized by the acute development of coughing, wheezing, shortness of breath, and decline in lung function. Asthma exacerbations are a significant source of morbidity and often necessitate emergent treatment

D. Cerrone · E. Gillett · S. Ward (✉)
Division of Pulmonology and Sleep Medicine, Children's Hospital Los Angeles, Los Angeles, CA, USA
e-mail: sward@chla.usc.edu

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in the outpatient setting with bronchodilators and systemic steroids. They are also associated with significant mortality with a rate of 0.02% in children and adolescents and of 1.9% in the elderly [3].

Through the use of guideline-driven diagnostic and treatment modalities, many patients are able to achieve control of their asthma and prevent asthma exacerbations which would otherwise often lead to costly outpatient medical visits or hospitalizations; however, despite guideline-driven care and adherence to therapy, many patients often remain symptomatic. Poor control is not a benign entity and is associated with an increased risk of exacerbations and the development of structural lung changes known as airway remodeling [4]. This has led to efforts to personalize therapy and investigate the mechanisms that inform the patient's disease. One arm of this method involves asthma endotyping whereby serologic and sputum samples from asthmatics are obtained in an effort to understand the inflammatory state of an asthmatic's airway. It has now become clear that different types of inflammation play a role in asthma and that different endotypes may respond to unique treatment options [5]. Another arm of personalization calls for a thorough examination of comorbidities that inform disease. Comorbidities in asthma are varied and include rhinitis, gastroesophageal reflux disease, and sleep disordered breathing to name just a few. It is the goal of this chapter to highlight the diagnosis and management of sleep disordered breathing in children with asthma through a review of recently published guidelines and peer-reviewed journal articles.

Nocturnal Asthma

Sleep poses a variety of physiologic challenges to the pediatric airway and lungs. An often overlooked challenge comes in the form of nocturnal asthma. Nocturnal asthma is the manifestation of asthma symptoms at night during periods of sleep. These very often include episodes of nocturnal cough, wheezing, and shortness of breath. Daytime symptoms as in sleepiness, behavioral problems, or school absenteeism may also manifest in light of poorly controlled or frequent symptoms. The pathophysiologic mechanisms that underlie nocturnal asthma are quite varied with both sleep-related physiology and circadian rhythm influences in play. Sleep is typically associated with a small decline in lung function with a nadir around 4:00 A.M. This nadir is exaggerated in the setting of asthma. Studies have revealed that this time period is characterized by decreased peak expiratory flow rates, decreased FEV_1, and increased airway hyperresponsiveness [6]. The aforementioned physiology in addition to aeroallergen sensitization, neurologic, and endocrine factors combine to form the nocturnal asthma phenotype.

Nocturnal asthma is not uncommon and a study from the Childhood Asthma Management Program calculated a prevalence of 33.7% among children with mild-moderate persistent asthma off maintenance medications. The study also found that atopy, peak flow variability, and severe asthma as defined by bronchodilator responsiveness were associated with a greater risk of nighttime awakenings [7]. Although

severe and uncontrolled asthmatics may be most affected, it is also known that well-controlled asthmatics are also at risk for sleep disturbances. One study compared well-controlled asthmatics with age and gender-matched non-asthmatic controls. The study found that 95% of controlled asthmatics had questionnaire-identified sleep disturbances. This included daytime sleepiness in 60% of the well-controlled group and difficulty in maintaining sleep in 38%. Controls had significantly less instances of sleep disturbance with 46.7% of controls identifying sleep disturbance on questionnaires [8]. This study highlights the point that all asthmatics, regardless of level of control, are at risk of sleep disturbances beyond nocturnal cough and frequent nocturnal awakenings. Clinicians need to be aware of this association. As severe asthmatics and uncontrolled asthmatics are likely to be disproportionately affected, it is important that all asthmatics are treated with guideline care with consideration of underlying comorbidities.

The condition is not benign and is associated with increased mortality. Statistics in children are sparse; however, a survey that studied asthma deaths over a 12-month period in a predominately adult population revealed that 53% of asthma-related deaths occurred at night [9]. Not surprisingly, the *Expert Panel Report of the National Asthma Education and Prevention Program* uses the frequency of asthma-related nocturnal awakenings as an identifiable and quantifiable factor in the classification of asthma severity. Per the Expert Panel Report, in children between the ages of 0 and 4 years, one or more episodes of nighttime symptoms are classified as persistent asthma with greater than one episode per week characteristic of severe persistent asthma. In children 5 years of age and greater, intermittent asthma is characterized by less than two episodes per month of nighttime awakenings, and severe persistent asthma is characterized by seven episodes per week [2]. These classifications are clinically useful as they help determine treatment regimens and are also an important factor in assessing control in those already diagnosed with asthma.

Asthma is diagnosed following a rigorous clinical assessment that includes a thorough history, physical examination, and pulmonary function testing. The assessment of nocturnal symptoms is inherently problematic, however. Practically speaking, neither a physical examination nor pulmonary function testing can be performed in a patient's home environment in the midst of nocturnal asthma symptoms. It has been thought that home spirometry may be useful in this setting; however, a recent study revealed that home spirometry poorly correlated with subjective assessments of asthma symptoms and was therefore limited in the management of child asthmatics [10]. History is also problematic as patients and their guardians may be unaware of child's nocturnal symptoms, indifferent to their existence or unclear as to what signifies a nocturnal symptom. Interestingly, however, clinicians should be aware that children are more likely to report the presence of nocturnal symptoms than are their parents [11]. These inconsistencies combine to create diagnostic and treatment dilemmas that will naturally have ramifications on management. Both child and parent education may help to alleviate some of the inconsistencies; however, an objective marker to assist in the quantification and grading of nocturnal symptoms may prove beneficial in the future [12].

Allegic Sensitization in Nocturnal Asthma and Obstructive Sleep Apnea

Allergic disease is not uncommon among children with asthma, and studies have found that exposure to certain allergens, namely, house dust mites, in early childhood may be a causative factor in the development of asthma [13]. Although the causal relationship linking allergen sensitivity to the development of asthma has yet to be fully defined, the effect of allergen sensitivity on diurnal asthma symptoms in childhood is well established in medical literature. In general allergic sensitization is associated with increased asthma morbidity, increased bronchial responsiveness, and increased asthma-related healthcare utilization. Urban populations appear disproportionately affected with pest sensitization associated with the greatest morbidity. A recent study evaluated the effect of pest sensitization in minority of children with asthma on asthma outcomes. The study revealed that mouse sensitization was associated with increased odds of an acute care visit and a threefold increased risk of hospitalization compared to those not sensitized [14]. The same study also revealed that nearly half of all children enrolled from New York were sensitized to either mouse or cockroach. These epidemiologic findings are not insignificant and suggest that care of poorly controlled asthma in urban youth may be optimized if allergic sensitivity to pests is recognized early and treated appropriately.

There have been more recent efforts to describe the effect of allergic sensitization on sleep outcomes. One study examined 96 children from urban areas with persistent asthma. These patients completed allergy testing and were followed for a 1 month period with actigraphy and home spirometry. In sum, 83% of the children had positive allergy testing with 61% sensitive to dust mites, 47% sensitive to spring trees, and 37% sensitive to mouse. The study revealed that patients with allergic sensitization had lower sleep efficiency and more nighttime awakening compared to those not sensitized. The study also found that those patients with more numerous positive test results were more likely to have more night awakenings compared to those with fewer results [15]. Once again, clinicians should be mindful of this association with a low threshold to obtain allergy testing in whom allergic disease is thought to inform poor nocturnal asthma control.

Although the association is less clear than in sleep disordered breathing and asthma, allergic sensitivity has been described in children with obstructive sleep apnea. A study examined 39 children age 1 to 7 years who were referred for polysomnogram for evaluation of snoring. The investigators sought to determine if allergic sensitization occurs frequently in children who snore and if allergy can be predictive of obstructive sleep apnea (OSA). Allergy testing was performed in all subjects followed by polysomnogram. In sum, 36% of this cohort of snoring children were found to be sensitized to aeroallergens. Fifty-seven percent of allergic subjects were found to have OSA, whereas 40% on nonallergic subjects were found to have OSA. The investigators concluded that allergic sensitization is frequently present in patients with habitual snoring and is associated with an increased risk of

OSA [16]. It remains unclear, however, if addressing allergic sensitization medically is beneficial in mitigating the severity of OSA.

Asthma and Sleep Hygiene

It is commonly known that asthma has a significant impact on sleep symptoms. Clinicians may be surprised to learn that the converse is also true whereby sleep may influence asthma symptoms. One study revealed that poor sleep quality in asthmatic children and adolescents is associated with more severe asthma symptoms the following day [17]. The results suggested that addressing poor sleep quality may in turn be beneficial in optimizing asthma control. Addressing sleep hygiene, for example, has been postulated as one such method in optimizing asthma control. Trials investigating the effect of optimized sleep hygiene in asthmatics have not been performed to our knowledge; however, it is clear that severe asthmatics have worsened sleep hygiene compared to non-asthmatics. This was demonstrated in a study which examined sleep duration, sleep hygiene, and insomnia in 298 adolescents through the use of validated questionnaires and reports. Of these 298 adolescents, 43 were identified as having severe asthma. This classification was made by questionnaire and was not confirmed through an investigation of individual medical records. Furthermore, patient-reported data as in sleep duration were not confirmed with objective parameters. The study revealed that over 40% of severe asthmatics reported insufficient weekday sleep. The study also revealed that nearly 40% of severe asthmatics in the study reported moderate to severe insomnia. This was double the rates seen in patients with non-severe asthma and no asthma history. In assessing sleep hygiene, severe asthmatics were more likely to sleep somewhere other than their own bed and were also more likely to use electronics at baseline compared to non-asthmatics [18]. The authors suspected that severe asthmatics have a tendency to sleep near their parents for fear of an asthma exacerbation. They further postulated that such behavior could lead to the development of sleep-onset association whereby the presence of a parent is necessary to facilitate sleep onset and to maintain sleep. In sum it can be said that poor sleep is associated with worsened asthma control. It can also be said that severe asthmatics specifically tend to have poor sleep hygiene and a significantly increased risk of clinical insomnia. The implementation of adequate sleep hygiene has been shown to increase sleep duration and decrease insomnia and depressive symptoms in non-asthmatic adolescents compared to controls [19]. It stands to reason that similar measures may prove beneficial in asthmatics. The American Thoracic Society has published recommendations regarding sleep hygiene and the sleep environment which apply to all children; however, an asthmatic may take additional steps which are likely to improve sleep and daytime symptoms [20]. These additional steps are included in Table 16.1 and include careful attention to the effects of aeroallergens and the sleep environment.

Table 16.1 Sleep hygiene and asthma. Simple steps to improve sleep in children with asthma

If possible, asthmatics should sleep alone in their own bed in a quiet darkened room
Minimize screen time, with no screen time within 2 hours before bed
Children should maintain the same bedtime and wake time from day to day with an age appropriate length of sleep time
Scents, perfumes, air fresheners, essential oils, and the like should not be used in the bedroom
Inhaled medications should be administered at the same time each day with a spacer. Administering an inhaled corticosteroid immediately prior to bedtime is unlikely to be more advantageous than scheduled administration during the afternoon
A rescue inhaler with spacer should be kept at the bedside in the event that cough, wheezing, or shortness of breath develops
Utilize dust mite and allergen proof pillow and mattress covers
Vacuum bedroom using a high-efficiency particulate air filter and wash bedding weekly
Pets should be kept outside the bedroom especially during sleep. If allergic, a HEPA filter should be running in the bedroom at all times
Screen for and eliminate pests (mice, cockroach, etc.) from the sleep environment if present
Shut windows when pollen counts are elevated
Shut windows during and after nighttime thunderstorms
If mold allergic, do not use humidifiers
The bedroom temperature should be neither cold nor excessively warm

Asthma and Sleep Disordered Breathing

Sleep disordered breathing is quite common in children with asthma. A recent systematic review evaluated 17 studies that assessed the association between asthma and sleep disordered breathing. In sum 45,155 patients were analyzed in total. The review revealed a 23.9% prevalence of sleep disordered breathing in asthmatics versus a 16.7% prevalence in non-asthmatics. The results suggested that sleep disordered breathing is nearly twice as likely to develop in an asthmatic compared to a non-asthmatic [21]. Through the years there has also been investigation into the association between asthma and sleep disordered breathing with some consideration that the association may be causal. This has been supported by the belief that the inflammatory pathophysiology that informs both conditions is quite similar. A recent study utilized the Bradford Hill criteria in assessing the causal relationship between asthma and sleep disordered breathing. The study found that many of the criteria espousing a causal relationship between asthma and sleep disordered breathing have been fulfilled in the medical literature. The criterion of temporality, however, has not been established and is a necessary factor in demonstrating causality [22]. Although a causal relationship has not been established, the association between asthma and sleep disordered breathing is quite strong with evidence that control of one entity is predicated upon control of the other. Optimizing treatment of either condition may prove beneficial in the treatment of the other.

Asthma Guidelines and Sleep Disordered Breathing

A number of guidelines have been drafted regarding the diagnosis and management of asthma in children. At present the two principal guidelines that guide asthma care worldwide are the Global Initiative for Asthma's *Global Strategy for*

Asthma Management and Prevention and the National Heart, Lung, and Blood Institute's *Expert Panel Report of the National Asthma Education and Prevention Program*. It is important to note that neither of these documents highlight the association between sleep disordered breathing and asthma in detail with the Global Initiative guidelines primarily highlighting the importance of assessing for obstructive sleep apnea in patients with uncontrolled asthma and severe asthma and in asthmatics with obesity [23]. The guidelines do not detail the specific assessment required; however, it can be inferred that pre-existing guidelines drafted for the purpose of the diagnosis and management of sleep-related breathing disorder should be followed.

Recognition and Treatment of SRBD: A Guideline Approach

Obstructive sleep apnea has historically remained an under-recognized diagnosis in children that, in recent years, has taken on increased importance in light of the obesity epidemic. The condition is common and may affect children of all ages with an estimated prevalence of 1–3%. Still more common is the diagnosis of primary snoring which carries a prevalence of 5–27% [24]. Obstructive sleep apnea is not a benign condition and is associated with cardiovascular morbidity, neurocognitive impairment, poor school performance, and reduced quality of life. Reassuringly, however, treatment options exist that are effective and often readily available in the community. Evidence suggests, however, that clinicians may be underdiagnosing sleep disorders in children including the diagnosis of obstructive sleep apnea. Efforts have thus been made to standardize the diagnosis and treatment of obstructive sleep apnea through the drafting of evidence-based clinical practice guidelines and practice parameters. The American Academy of Pediatrics (AAP), the Academy of Otolaryngology-Head and Neck Surgery, and the American Academy of Sleep Medicine have published such documents which will be reviewed here.

Screening

Screening patients for obstructive sleep apnea is entirely clinical and can be completed with a thorough history and physical examination. All children regardless of age and underlying morbidity warrant screening. Screening begins with a detailed history that includes an inquiry into the presence of snoring. Snoring is itself not diagnostic of obstructive sleep apnea and may be associated with the more common diagnosis of primary or habitual snoring. The condition is not associated with the disruption of ventilation and sleep patterns characteristic of obstructive sleep apnea but is itself associated with adverse neurobehavioral outcomes as in hyperactivity and poor school performance [25]. Obstructive sleep apnea, however, is often associated with other symptoms that include morning headache, daytime sleepiness, inattention, hyperactivity, learning difficulties, and sleep enuresis to name a few.

The History

In the American Academy of Pediatrics (AAP) clinical practice guideline, *Diagnosis and Management of Childhood Obstructive Sleep Apnea Syndrome*, an inquiry into the presence of childhood and adolescent snoring is recommended [26]. If the response is affirmative, the guideline recommends a more focused evaluation which includes a detailed history and physical examination. The history should attempt to quantify the frequency of snoring and should identify other sleep-related behaviors which may be associated with obstructive events as in gasping, choking, labored breathing, or witnessed apneas. A detailed history should also include an investigation into parasomnias and daytime symptoms as in daytime sleepiness and inattention, all of which can be increased in pediatric OSA. Clinicians should be careful not to rely on the finding of daytime sleepiness alone in their assessment. Although this may be seen in children it is actually more commonly seen in adults with OSA. A more reliable feature is that of hyperactivity which is the most common behavioral abnormality encountered in children with sleep disordered breathing [27]. In fact, snoring may itself be a risk factor for the development of hyperactivity [28]. The aforementioned daytime symptoms may be so stark that a diagnosis of attention deficit hyperactivity disorder (ADHD) may be rendered with the symptoms resolving only after treatment with adenotonsillectomy [29].

In considering asthma patients, it may be advantageous to screen for predictors of habitual snoring and obstructive sleep apnea. A number of these predictors have been identified. A study of 244 asthmatics identified that 37% of patients snore habitually with the presence of gastroesophageal reflux disease and use of inhaled corticosteroid predictive of this [30]. An increased risk of obstructive sleep apnea as defined by a questionnaire was predicted by asthma severity and inhaled corticosteroid use. The authors also identified female gender as a risk factor that carried with it a 111% greater risk for OSA in comparison to a male with asthma. The study was limited by the fact that polysomnography was not utilized to confirm the diagnosis of habitual snoring or obstructive sleep apnea. Although limited in this regard, clinicians should be mindful that asthmatics with GERD and on inhaled corticosteroid are at increased risk of sleep disordered breathing and should be screened carefully with further history and exam.

Questionnaires

Questionnaires have been developed to aid clinicians in the screening of sleep disordered breathing. One such document is the Pediatric Sleep Questionnaire (PSQ) [31]. This 22-item questionnaire is validated in children 2–18 years of age and contains questions that assess a variety of factors that include the severity of snoring, the presence of daytime symptoms as in sleepiness and morning headaches, and the presence of abnormal daytime behaviors as in inattention and hyperactivity. The questionnaire has a sensitivity of 85% and a specificity of 87% for sleep-related breathing disorders. The PSQ was further validated in patients with polysomnography-proven obstructive sleep apnea. A high score was found to predict a threefold

risk for OSA on polysomnography and a twofold risk for residual OSA 1 year following adenotonsillectomy [32]. It must be stressed that this and other questionnaires are not sufficient to diagnose obstructive sleep apnea, and the AAP suggests that they may be used as a screening tool where a negative result is unlikely to label a patient with OSA as being healthy [33]. As regards children with asthma, the PSQ was validated retrospectively in a cohort of 160 children with primarily poorly controlled asthma. The study revealed that the PSQ has a rather good sensitivity (up to 81.6% when considering asthmatics with an AHI cutoff of 1.0) but a poor specificity [34]. Once again, the results suggest that the PSQ may function as a reasonable first-line screening tool but is in no way sufficient for the diagnosis of OSA.

Physical Examination

The AAP guidelines also stress the importance of the physical exam which should include careful attention to a patient's habitus, tonsillar and tongue size, palate, and facial and jaw anatomy. Features of concern that are associated with obstructive sleep apnea include an overweight body habitus, tonsillar enlargement, macroglossia or glossoptosis, palatal clefts or high-arched palate, midface hypoplasia, and micrognathia. A neurologic examination assessing the presence of tone is also important as generalized hypotonia may predispose to obstructive events. Finally, careful attention to a patient's blood pressure may be telling as both elevated daytime and nocturnal blood pressures are associated with untreated obstructive sleep apnea [35].

When to Order a Polysomnogram

If a child or adolescent is noted to snore on a regular basis and has any of the aforementioned symptoms or exam findings, then the AAP recommends proceeding with a sleep study or referring the patient to a sleep specialist or otolaryngologist. The guidelines also note that resources may be limited in communities, and for this reason alternative modalities such as nocturnal oximetry or daytime nap polysomnography may be of use if an overnight polysomnography study cannot be obtained. A nocturnal oximetry study, for example, may be a cost-effective and easily obtainable option for patients. This modality is limited and is not itself sufficient to diagnose OSA. This was demonstrated in a prospective cohort study in which children age 4 to 18 years underwent two nights of nocturnal oximetry monitoring and a third night of polysomnography. The oxygen desaturation index calculated from the nocturnal oximetry studies agreed poorly with the apnea hypopnea index calculated on the overnight polysomnogram. With a desaturation index of more than 5 per hour, the sensitivity of oximetry for identifying children with moderate OSA was of 66.7% and a specificity of 60% [36]. The low sensitivity and specificity may be secondary to the fact that the AHI is informed by arousals and awakenings in addition to oxygen desaturations.

The AAP screening guidelines are widely generalizable; however, certain conditions are associated with an elevated prevalence of obstructive sleep apnea and warrant special attention. *Practice Parameters for the Respiratory Indications for*

Polysomnography in Children were drafted in 2010 and approved by the American Academy of Sleep Medicine [37]. These recommendations highlight these conditions and stress that clinicians should consider obtaining a sleep study in patients affected by them if there is the slightest suspicion of sleep-related breathing disorder. These conditions include obesity, trisomy 21, Prader-Willi syndrome, neuromuscular disorders, Chiari malformations, myelomeningocele, and craniofacial anomalies. Trisomy 21, for example, is not uncommonly managed in a general pediatric clinic. This condition is associated with relative macroglossia, midface hypoplasia, and hypotonia which combine to predispose patients to obstructive sleep apnea. In fact, the prevalence of obstructive apnea in this population may be higher than that in any other genetic condition with a prevalence rate of 66.4% [38]. Given the increased prevalence and the poor correlation between sleep studies and parental reports, the AAP recommends that all children with trisomy 21 should have a sleep study by 4 years of age [39]. Realistically, however, if a patient is symptomatic before age 4, then a sleep study should be obtained sooner. It is also worth mentioning that the prevalence of wheezing and rhinitis in patients with trisomy 21 is increased compared to healthy siblings and age- and sex-matched controls. Although wheezing prevalence is increased and was cited as 18.5% in one cohort of children with trisomy 21, the risk of asthma is not [40]. The true prevalence of asthma is unclear in this population which is likely secondary to an inability of some patients with trisomy 21 to reliably perform pulmonary function testing. Clinicians should be mindful of this limitation and should screen for asthma in patients with trisomy 21 with a thorough history that attempts to quantify wheezing and nocturnal symptoms and gauge overall exercise tolerance.

The American Academy of Otolaryngology-Head and Neck Surgery drafted clinical practice guidelines in 2011 for otolaryngologists which echo the aforementioned practice parameters and add that patients with sleep disordered breathing and the diagnosis of obesity, trisomy 21, craniofacial abnormalities, neuromuscular disorders, sickle cell disease, or mucopolysaccharidoses should have a polysomnogram prior to tonsillectomy [41]. The recommendation for a polysomnogram is also recommended in patients for whom the need for surgery is uncertain or in whom there is discordance in tonsillar size and the severity of sleep disordered breathing. It is easy to assume, for example, that those patients without hypertrophied tonsils are unlikely to have obstructive sleep apnea and therefore do not require tonsillectomy. This may be the case; however, in the setting of sleep disordered breathing, small tonsils, and an abnormal polysomnogram, the removal of the tonsillar tissue may still prove beneficial [42]. For this reason, if discordant findings are present, a sleep study ultimately is recommended.

Treatment with Adenotonsillectomy

The AAP guidelines recommend proceeding with adenotonsillectomy if a child is determined to have OSA, has a clinical examination consistent with adenotonsillar hypertrophy, and does not have a contraindication to surgery. In general,

adenotonsillectomy is an effective strategy in treating OSA in children. The efficacy of the therapy was recently highlighted in a multicenter retrospective review that examined both preoperative and postoperative polysomnograms. A total of 578 children were analyzed with a mean age of 6.9 years, mean BMI z-score of 1.35, and mean pre-op AHI of 18.2. Of note, just over 50% of the children were noted to be obese and 29.6% of children were asthmatic. After tonsillectomy repeat polysomnograms revealed a mean AHI of 4.1 with 27.2% of patients having complete resolution of OSA. The study also revealed significantly improved sleep efficiency. Advancing age, increasing BMI z-score, presence of asthma, and a significantly elevated preoperative AHI were associated with residual obstructive sleep apnea [43].

In light of the increased risk of residual OSA and the increased risk of intraoperative and postoperative complications in the setting of asthma, some clinicians may be apprehensive about proceeding with adenotonsillectomy. This concern is reasonable; however, the benefits of the surgery extend beyond sleep symptoms alone and may improve overall asthma control. A robust retrospective database review studied the impact of adenotonsillectomy on the rates of asthma exacerbations and status asthmaticus. Over 13,000 children with the diagnosis of asthma and a history of tonsillectomy were included. The authors compared outcomes in patients 1 year prior to surgery and up to 1 year following surgery. The authors also included over 27,000 age-, sex-, and geographically matched patients with history of asthma without adenotonsillectomy for comparison. In sum, adenotonsillectomy was associated with a 30.2% reduction in asthma exacerbations and 37.9% reduction in status asthmaticus. The investigators also found that adenotonsillectomy was associated with fewer prescription refills [44]. A prospective study was also recently published and is worth mentioning. The investigators hypothesized that as asthma and OSA are both inflammatory disorders, the treatment of OSA would reduce the frequency of asthma exacerbations in poorly controlled asthmatics with OSA. Ninety-two poorly controlled asthmatics aged 3–10 were enrolled. These patients underwent polysomnography which revealed moderate or severe OSA in 58 patients. These patients had a mean AHI of 14.6 and BMI z-score of 1.46 ± 1.32. Data following adenotonsillectomy was available in 35 patients. Prior to surgery these patients were noted to have 4.1 asthma exacerbations per year on average. Following surgery this frequency reduced to 1.8 per year and was of statistical significance. These patients also had statistically significant reduction in weekly rescue inhaler use and asthma symptom score. The investigators also found statistical improvement in FEV_1 following surgery with an increase from 80.1 to 86.5 percent predicted [45].

The AAP guidelines identify a number of risk factors for postoperative respiratory complications in children undergoing adenotonsillectomy. These include children younger than 3 years of age, severe OSA, patients with cardiac complications secondary to OSA, failure to thrive, obesity, craniofacial anomalies, neuromuscular disease, and current respiratory infections. It is recommended that patients in whom any of these factors are identified should be admitted to the hospital postoperatively for observation. These recommendations are also echoed by the American Academy of Otolaryngology-Head and Neck Surgery. It is important to note that asthma is not

included in this list; however, asthma is itself associated with a number of intraoperative and postoperative complications including laryngospasm and bronchospasm. It is important that all patients with asthma be assessed by an anesthesiologist in advance of the procedure. Ideally asthma control should be optimized well before the procedure, and pending on a patient's lability, a course of preoperative prednisone may be warranted to prevent complications. Specific guidelines regarding the use of prednisone perioperatively are nonexistent, and pediatric studies are also lacking. If there is evidence of significant intraoperative bronchospasm, persistent wheezing postoperatively, or any further evidence of respiratory distress, then it would seem reasonable to proceed with hospitalization for management.

Treatment with Nasal Steroids

The AAP guidelines state that clinicians have the option of prescribing topical intranasal corticosteroids in children with mild OSA in whom adenotonsillectomy is contraindicated or in children with mild postoperative OSA. Intranasal steroids have been shown to reduce both the severity of mild OSA and the adenoidal nasopharyngeal ratio. Interestingly, the same study revealed that the findings lasted at least 8 weeks after cessation of therapy [46]. It should be stressed that childhood asthma is strongly associated with allergic rhinitis with half of all asthmatics carrying the diagnosis. In addition to oral and intranasal antihistamines, intranasal steroids are considered an important treatment modality. In light of this overlap, it would seem reasonable to treat concomitant allergic rhinitis in asthmatics with mild OSA with an intranasal steroid to target treatment of both atopy and OSA.

Treatment with Montelukast

Montelukast is a leukotriene receptor antagonist that is approved as a maintenance therapy for the treatment of asthma in the United States. It remains an important component of asthma management in children and may be initiated as an alternative to low-dose corticosteroid in step two treatment of mild persistent asthma. It may also be added in addition to inhaled corticosteroids in more advanced steps. As regards OSA, it has been demonstrated that the cysteinyl leukotriene receptor-1 is overexpressed in the adenotonsillar cells in children with OSA [47]. This has led some to believe that treatment with a leukotriene receptor antagonist as in montelukast may be of benefit in the treatment of OSA. There have been a select number of nonrandomized, open-label studies assessing the benefit of montelukast in OSA. One study revealed small but significant decrease in the AHI of children with mild OSA [48], and another revealed similar findings in children with residual OSA treated with intranasal steroids and oral leukotriene modifier therapy [49]. The AAP clinical practice guidelines do not specifically note montelukast although the guideline's technical report highlights that data is insufficient to recommend treatment of OSA with the medication. Since the publication of the AAP guidelines in 2011, two

additional double-blind, placebo-controlled studies have been published which are worth noting. The first published in 2012 recruited 46 children with habitual snoring and diagnosis of non-severe OSA on polysomnography [50]. Twenty-three children were assigned to 12 weeks of treatment with montelukast, and 23 were assigned to 12 weeks of placebo. Parent questionnaires and lateral neck radiographs were also obtained prior to the study and at the conclusion of the study. Finally, all children were studied by polysomnogram at the conclusion of the study. The study revealed that compared to placebo the montelukast group had a decrease in the AHI by roughly half and a significant decrease in adenoid size as well. A more recent study published in 2016 revealed similar findings utilizing a 16-week treatment course of montelukast [51].

The studies in sum suggest that montelukast is both a safe and effective treatment for mild to moderate OSA. Asthmatic patients may undoubtedly benefit from this medication both from the standpoint of treating underlying asthma and treating mild to moderate OSA. For purposes of asthma, montelukast has been validated as a safe and effective maintenance therapy that may be continued indefinitely in treatment plans. It remains, unclear however, if montelukast can suppress adenotonsillar hypertrophy beyond 16 weeks. It is also unclear how treatment with montelukast compares to adenotonsillectomy in children. Further studies, especially studies evaluating the efficacy of montelukast in asthmatics with OSA, are warranted.

Postoperative Follow-Up

The AAP guidelines recommend clinical reassessment approximately 6 to 8 weeks after surgery. Clinicians should inquire about the presence of snoring and investigate for the presence of daytime symptoms. If residual symptoms are identified, a clinician should proceed with objective testing as in a repeat polysomnogram. The guidelines also recommend that patients with a significantly abnormal baseline polysomnogram and obese patients should also undergo a repeat polysomnogram. The diagnosis of asthma is not specifically delineated as a reason for repeating a polysomnogram; however, clinicians need to be aware that asthmatics are at an increased risk of residual OSA compared to otherwise healthy non-obese children. It is thus important to obtain a routine sleep history at all clinical encounters from children with asthma who have undergone adenotonsillectomy.

Asthma and CPAP

Continuous positive airway pressure or CPAP is a therapy whereby a continuous pressure is applied in an effort to stent the airway open and prevent airway collapse. The AAP recommends CPAP in patients with diagnosis of OSA in whom adenotonsillectomy is not performed or in patients in whom symptoms or evidence of OSA persists despite adenotonsillectomy. The therapy is safe, inexpensive, and readily available in many communities. The effects of CPAP in children with asthma and OSA have not

been readily described in medical literature. A number of studies, however, have posited a beneficial role for the therapy in adult asthmatics with OSA. In one study a total of 43 patients with poorly controlled nocturnal asthma per Global Initiative for Asthma guidelines were studied with pulmonary function testing, nocturnal asthma symptom scores, and polysomnography. Those patients with an AHI in excess of 15 were treated with CPAP for 2 months at which point pulmonary function testing and a symptom score were repeated. The study revealed a significant improvement in nocturnal symptom score compared to baseline but no significant change in pulmonary function testing [52]. A large prospective multicenter study was recently completed which extended the observation period beyond 2 months to 6 months. The study enrolled a total of 99 participants with a mean age of 57 years with a respiratory disturbance index (RDI) greater than or equal to 20 with diagnosis of asthma. Baseline pulmonary function testing, an Asthma Control Questionnaire, Mini Asthma Quality of Life Questionnaire, and questions regarding GERD symptoms were evaluated. At the 6-month period after treatment with CPAP, asthma control and quality of life were found to be significantly improved in those with moderate-severe persistent asthma. FeNO, bronchodilator responsiveness, and symptoms of GERD were also found to be improved at the 6-month mark in all asthmatics [53].

Although CPAP was found to be beneficial in reducing asthmatic symptoms in the setting of OSA, the question has also been raised if CPAP may reduce asthma symptoms in the absence of OSA. Interestingly, this therapy was actually found to not be beneficial in a study in seven asthmatics without OSA and was associated with worsened sleep architecture with increased awake time and decreased REM sleep [54].

Conclusions

Asthma and sleep disordered breathing remain highly prevalent conditions associated with tremendous morbidity in the pediatric population. Clinicians may be familiar with managing these conditions in isolation, and guidelines have been drafted to assist clinicians in this effort. The task of managing the two conditions together poses a unique challenge, however, where control of one entity is predicated on the control of the other. This comorbidity balancing act is a veritable challenge that is not fully addressed in either asthma or sleep disordered breathing guidelines. It has been the goal of this chapter to highlight current guidelines with an eye to emerging evidence that may allow clinicians to optimize the treatment of asthma and sleep disordered breathing in unison.

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Part IV

Allergic Rhinitis

Pathophysiology of Sleep-Disordered Breathing and Allergic Rhinitis

17

Fatima S. Khan

Allergic rhinitis is defined as an inflammatory condition of the nasal mucosa primarily triggered by IgE to aeroallergens in the environment [1]. Both indoor and outdoor allergens such as pet dander, dust mites, molds, and pollens can cause allergic rhinitis. Symptoms consist of nasal congestion, sneezing, nasal drainage, and nasal pruritus. Symptoms may occur seasonally or perennially depending on the trigger. It is not uncommon to have multiple allergen triggers. There are other non-allergic causes of rhinitis such as irritant, drug induced, hormonal, and infectious, but I will focus solely on allergic rhinitis in this chapter.

Allergic rhinitis is estimated to affect about 60 million people in the United States [2], approximately 40% of whom are children [3]. Allergen sensitization may begin in the first year of life manifesting as an inflammatory skin condition known as atopic dermatitis. It progresses to allergic rhinitis and subsequent development of asthma. This linear progression has been dubbed "the allergic march" [4, 5]. Most children become symptomatic with allergic rhinitis by 6 years of age [2]. There are other associated comorbidities; 38% of patients with allergic rhinitis also have concomitant asthma, whereas 78% of patients with asthma also have allergic rhinitis [6]. Forty-three percent of 4- to 17-year-olds with allergic rhinitis also have sinus disease [7, 8]. Furthermore, surveys conducted reveal 80% afflicted with allergic rhinitis experience fatigue, and approximately 2/3 felt irritable [2]. The symptoms of allergic rhinitis can adversely affect athletic performance and activities of daily living [2, 9]. Children with allergic rhinitis experienced otitis media with effusion more often than their non-allergic peers [10, 11] especially during their allergy season. They are twice more likely to undergo surgical intervention (i.e., tympanostomy tubes or adenotonsillectomy) than their peers without allergies [7]. Approximately 88% of children with allergic rhinitis also have some degree of sleep

F. S. Khan (✉)
Department of Allergy and Immunology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: FSKhan@luriechildrens.org

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impairment [12]. Children with allergic rhinitis have an almost twofold increase in visits to their healthcare providers and similar increase in medication costs [13]. Treatment of allergic rhinitis costs approximately $11.2 billion annually [3]. This expense estimate has steadily increased since 1995 and includes medications, provider visits, and treatment complications (i.e., otitis media, sinusitis, surgery) [3, 14]. Allergic rhinitis can place a significant financial burden on the entire family.

Allergic Rhinitis Symptoms

Allergic rhinitis symptoms also negatively impact the quality of life of the child and their family. In addition to nasal congestion, pruritus, and mucus drainage, symptoms may also include sinus pressure, headaches, otalgia, cough, and sleep disturbances. Coughing occurs due to increased afferent nerve reactivity mediated by histamine but also secondary to direct laryngeal stimulation by mucus [15]. Sleep impairment occurs more often in these patients. Gentile surveyed patients with allergic rhinitis and found approximately 78% had poor sleep quality, 75% were unable to fall asleep, and 64% reported waking during the night [3, 16]. Both children and adults with moderate to severe allergic rhinitis reported increased daytime somnolence, fatigue, and sleep disturbance [17]. There are many factors contributing to sleep disturbance. Sleep may be affected by the discomfort of the symptoms, postnasal drainage, and medication side effects and also due to various degrees of obstruction to airflow. Children with allergic rhinitis are at higher risk for adenotonsillar hypertrophy [18].

Adenoid and tonsillar hypertrophy are commonly associated with allergic rhinitis [19]. Recurrent otitis media, sinusitis, and airflow limitations associated with adenotonsillar hypertrophy can cause snoring. Severity of obstructed breathing can range from snoring to obstructive sleep apnea syndrome. Children with obstructed breathing have a higher prevalence of allergies [20, 21]. Simply snoring alone, without apnea, is sufficient to affect sleep quality [22]. Blunden's group assessed neurocognition in school-age children who snore. Snoring alone affected school performance adversely. Children who snore have microarousals during sleep [23] and increased time to REM sleep. Progression through the stages of sleep and less time in REM are key factors affecting cognition [24]. Poor sleep quality can significantly impact growth, concentration, and learning [25]. Sleep-disordered breathing may also adversely affect a child's behavior. Attention deficit hyperactivity disorder is also present more often in children with sleep-disordered breathing [19]. Presenteeism has been reported due to these sleep disturbances; students with daytime somnolence have poor concentration and poor learning [26].

Poor sleep or fragmented sleep, secondary to allergic rhinitis, is also associated with missing school and productivity losses [13, 27]. Children may lose up to 2 million days of school per year [2, 13, 27]. Productivity losses due to missed school and work days add to the burden of this disease. It is the unseen impact of allergic rhinitis that may be overlooked or not assessed in this condition.

Anatomy

No discussion of allergic rhinitis is complete without a review of the human nasal and sinus anatomy. The human skull contains four air-filled cavities called sinuses pictured in Fig. 17.1. The frontal sinus is located in the forehead. There are two maxillary sinuses within the cheeks, ethmoid sinuses located within the bone that resides in the medial corner of each eye and the sphenoid sinus which sits behind the ethmoid [28, 29]. The sinus anatomy differs in children compared to adults. Children have maxillary and ethmoid sinuses at birth, but pneumatization occurs by 7 years of age. The sphenoid sinus is first radiographically visualized at 9 months and begins aerating at 3 years of age. Frontal sinuses are not present at birth. They develop slowly and are present on imaging by 5 years [30]. The sinuses develop in the following sequence: the ethmoid first and then maxillary and sphenoid, and frontal sinus is the last to develop. Pneumatization of the sinuses occurs in two stages from birth to 4 years and a second wave from 8 years onward. Sinus development is completed by 18–20 years of age [31].

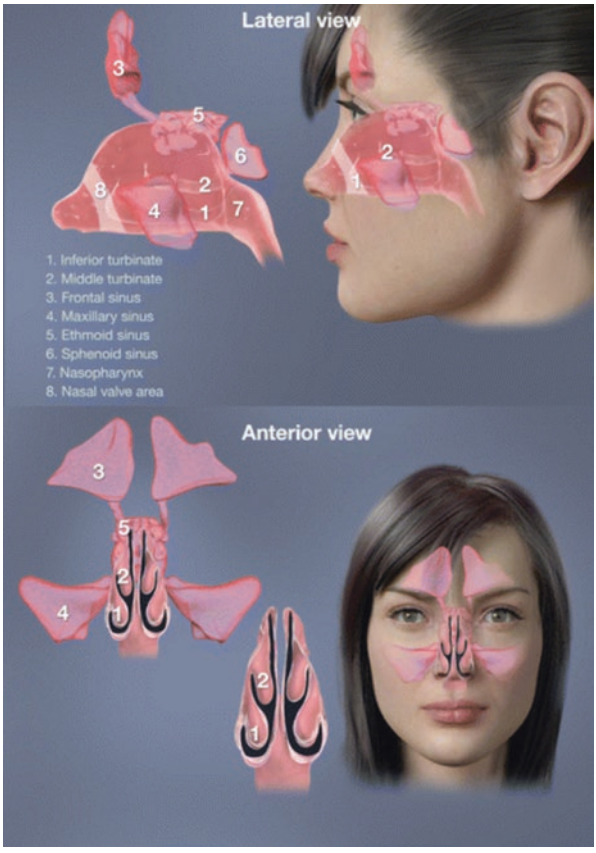


Fig. 17.1 Nasal and sinus anatomy. (Adapted from Djupesland [63], with permission)

The sinuses are lined with mucosa consisting of squamous epithelial cells that produce mucus containing IgA. This mucus drains into the nasal cavity. These epithelia also line the anterior nose and turbinates. The nose is comprised of cartilage separated into two nostrils by the nasal septum. The upper part of the septum consists of the ethmoid bone, vomer, maxilla, and palatine bones. The remaining 2/3 consists of quadrangular cartilage. The lateral nasal walls form the sides of the nose and contain three bony projections called turbinates. They are lined by mucosa. The inferior turbinate is the largest and lowest. It is responsible for the majority of warming, humidification, and conditioning of the air prior to entry into the lungs. The inferior turbinate is the only one that is a separate bone attached to the lateral wall. Above it lies the middle turbinate comprised of the ethmoid bone. The superior turbinate lies above the middle and also arises from the ethmoid bone. Each sinus drains into the nasal cavity via small openings called meatus. The sphenoid and posterior ethmoid sinuses drain into an area of the superior turbinate called the sphenoethmoid recess. The frontal and anterior ethmoid sinuses drain into the middle meatus of the middle turbinate [28, 29].

The nasal passage diameter can be affected by increased mucus production, mucosal edema, and enlargement of the turbinates. The nasal passage naturally narrows at a point called the nasal valve (Fig. 17.2). It is anterior to the inferior turbinate and causes natural resistance to airflow. The nasal valve contributes 50% of the resistance to airflow [19]. Nasal pathology, turbinate edema, adenoid hypertrophy, and nasal septal deviation can all adversely affect airflow. Mucosal edema and turbinate hypertrophy narrow the nasal passageway further limiting the flow of air. Turbulence is created by obstruction to flow and prompts paradoxical narrowing in the nasopharyngeal space. This further restricts airflow through the nasal valve compounding the problem. The Bernoulli effect from physics applies here. The airway paradoxically narrows as airflow velocity increases. Increased nasal resistance initiates decreased airflow. In addition, during sleep, the pharyngeal muscles normally relax and the airway narrows, thus amplifying the anatomic pathology of allergic rhinitis. Adenotonsillar hypertrophy and nasal mucosal edema caused by allergic rhinitis worsen airway narrowing and adversely impact sleep quality.

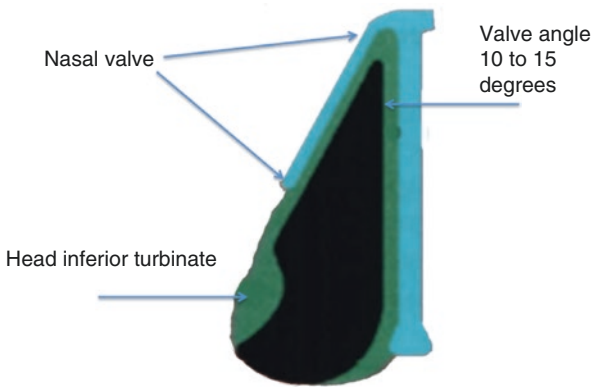


Fig. 17.2 Nasal valve angle

Sleep Architecture in Children

Research is ongoing to understand sleep architecture in children. Sleep is essential for normal growth, development, and neurologic function. Sleep is regulated by our circadian rhythm and daylight cues from our environment [32]. Total sleep time varies and changes with age. Newborns develop their circadian rhythm based on ambient light cues during the first months of life. They spend a total of 16–18 hours a day sleeping. Total sleep time decreases to 14–15 hours per day by 1 year of age [33]. This pattern continues as children grow. Total sleep time decreases steadily to about 11 hours by 5 years of age [32].

Normal sleep is divided into four stages. Figure 17.3 demonstrates normal sleep EEG in a child. The amount of time spent in each stage and the total sleep time required varies with age. Stage 1 is nonrapid eye movement (NREM) sleep. It is the lightest stage of sleep. The child is drowsy but can be easily roused during this stage. Children spend approximately 2–5% of total sleep time in this stage. In stage 2, sleep deepens and half of total sleep time is spent in this stage. Stages 3 and 4 are similar to each other. They are referred to as slow-wave sleep (SWS) or delta wave based on the EEG pattern typically seen during this stage. Children are in a deep stage of sleep and difficult to arouse. They spend roughly 20% of their time in this stage. REM (rapid eye movement) sleep occurs after stages 3 and 4. It is the most active phase of sleep with the highest EEG activity. Peripheral muscle paralysis occurs during REM sleep and rapid eye movement occurs in bursts [32]. Dreams occur during this stage and can be recalled when awake. Information from the day is processed during REM sleep. Learning occurs, neural pathways are strengthened,

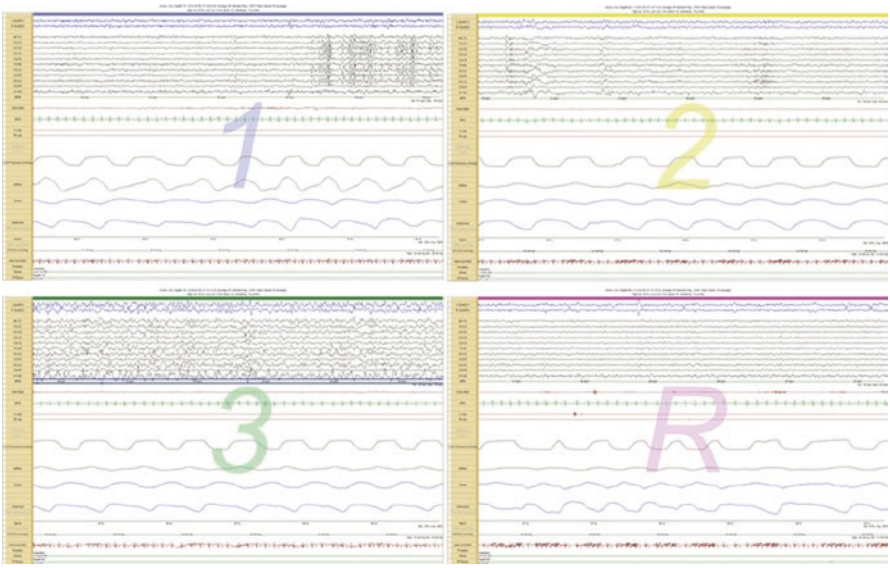


Fig. 17.3 Normal sleep EEG. (Courtesy of Jeremy Yob)

and memory is made [34]. Infants spend about 55% of their total sleep time in REM sleep, but this amount declines to about 20–25% by age 5 years. Disruption of sleep during these four stages can affect entry into and time spent in REM sleep. Quality of REM can impact neurocognitive health.

Using polysomnography, sleep was studied in children with ADHD and healthy matched controls. Standardized tests of IQ were conducted during the study. The group found REM sleep quality inversely affected IQ scores [35]. Quality of REM sleep correlated with IQ scores. Children with sleep-disordered breathing also scored low on IQ tests used during the study. Miano et al. also demonstrated decreases in IQ scores in children with obstructive sleep apnea syndrome [36]. Obstructive sleep apnea also increased sleep disturbance and decreased time spent in the early stages of sleep [37]. These children had increased latency to REM sleep and, therefore, reduced time in REM [36]. Hypoxia and other respiratory events that occur in obstructive sleep apnea cause sleep fragmentation and have adversely affected neurocognition and behavior [38]. Snoring alone, without apneic events, also adversely affects sleep quality and neurocognition in children [22].

Hyperactivity, inattention, and daytime somnolence were seen in children with sleep-disordered breathing and adenotonsillar hypertrophy [39]. Attention, memory, and sleepiness were assessed using several standardized tools: Conners' questionnaire, children's symptom inventory, children's memory scale, and multiple sleep latency test. Children who underwent adenotonsillectomy were reassessed 1 year after surgery and demonstrated statistically significant reversal of behavioral effects [40].

There are several notable changes occur at the cellular level in allergic rhinitis. Allergic rhinitis is an IgE-mediated condition. Repeated exposure to an environmental aeroallergen leads to the production of IgE antibody. IgE binds to the high-affinity FCERI receptor on the surface of mast cells triggering their degranulation. This leads to the release of histamine and several preformed mediators which cause inflammation, edema of the tissue, and mucus production. This process begins with allergen sensitization. Antigen is picked up and presented to a naïve T lymphocyte via an antigen-presenting cell (APC). T cells differentiate into Th2 cells upon stimulation by TSLP (thymic stromal lymphopoietin) and other cytokines (IL-4, IL-5, IL-13). Th2 cells that bind to B cells via major histocompatibility complex class II (MHCII) secrete IL-4 and IL-13. They induce the B cell to undergo class switching and produce IgE specific to the antigen. IgE binds to high-affinity FCERI on the mast cell surface and triggers degranulation via cross-linking with antigen. The presence of IgE binding further stabilizes and increases FCERI receptors on the mast cell surface [41, 42]. Th2 cells are the main drivers of the allergic pathway. They also release a variety of cytokines that are crucial for growth and chemotactic factors for granulocytes that are involved in the pathology associated with allergic rhinitis. Dendritic cells release TSLP (thymic stromal lymphopoietin) which attracts Th2 cells to the tissue and promotes dendritic cell maturation into type 2 cells [3]. Th2 cells are capable of picking up the processed antigen from antigen-presenting cells. In response, they release GM-CSF (granulocyte-macrophage colony-stimulating factor), IL-4, IL-5, and IL-13. GM-CSF promotes stem cells to

differentiate into eosinophils and basophils [43]. Basophils also have FCERI on their surface. They also release IL-4, IL-5, IL-6, and IL-9 promoting survival and maturation of eosinophils and basophils. IL-6 is an inflammatory cytokine also involved in pyrexia. Eosinophils release IL-3 and IL-5. IL-3 is important for basophil survival and a growth factor for mast cells.

Figure 17.4 shows the immunological events that occur in the mucosa. Mast cell degranulation involves release of preformed mediators (tryptase, chymase, carboxypeptidases) and histamine. Four histamine receptors have been characterized: H1, H2, H3, and H4. Histamine acting via H1 receptors triggers smooth muscle contraction, bronchospasm, and increased endothelial permeability [3]. It also stimulates cough receptors. Mast cells also synthesize and release leukotrienes LTB4, LTC4, and LTD4, prostaglandin PGD2, platelet-activating factor (PAF), and IL-3, IL-4, and IL-5. PGD2 stimulates smooth muscle contraction along with PAF. LTB4 and PAF stimulate neutrophil chemotaxis, while the cytokines activate mast cells, eosinophils, and basophils. All of these cytokines reinforce and promote ongoing allergic inflammation.

These cytokines induce change in the cellular milieu of the nasal mucosa in allergic rhinitis.

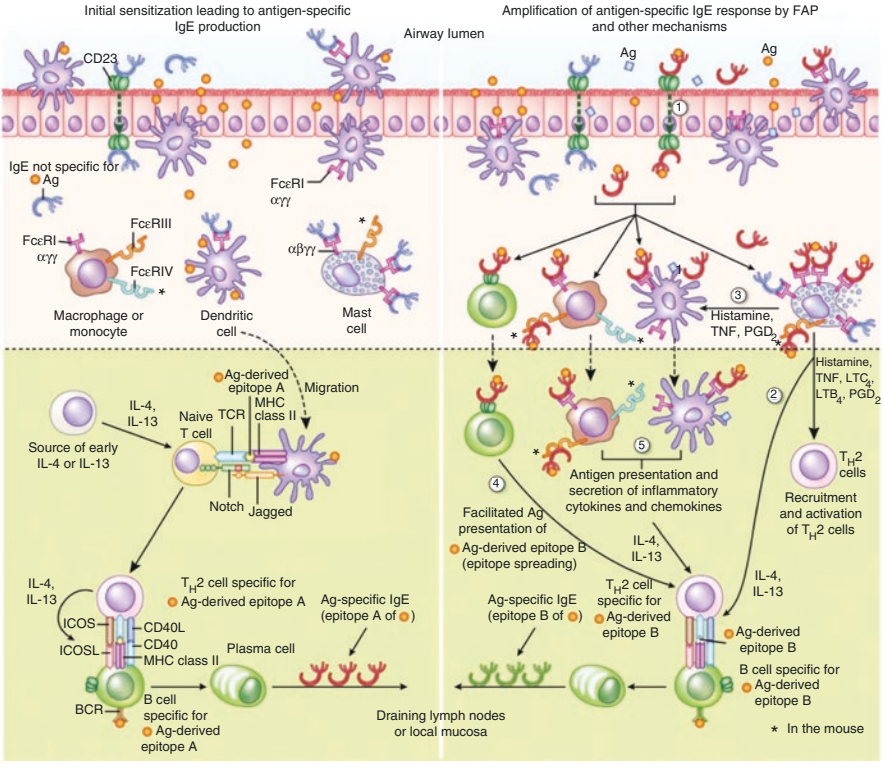


Fig. 17.4 Allergen sensitization and IgE production. (From Galli and Tsai [42], with permission)

There is an early and late phase response to allergen exposure at the mucosal level. The early phase response occurs within minutes of nasal allergen exposure and peaks by 30 minutes post exposure. Symptoms are mediated by histamine released from mast cells after IgE cross-linking of FCERI receptors [44] causing rhinorrhea, pruritus, sneezing, and turbinate edema. Histamine levels fall and then gradually rise leading into the late phase reaction. This phase involves T cells, basophils, and eosinophils that have been recruited to the nasal mucosa. Repeated exposure to allergen triggers the late phase reaction beginning within 6 hours post allergen exposure. Eosinophils are the main cell type involved in the late phase reaction. Eosinophils are found in increased numbers in the nasal mucosa. Nasal symptom severity has been linked to increased influx of eosinophils in the mucosa [45]. Figure 17.5 demonstrates the cells within the nasal mucosa of a patient with allergic rhinitis.

The nasal epithelium, like the epidermis of the skin, is a continuous layer with tight junctions forming a barrier to the entry of pathogens and antigens. Dendritic cells are also present in the skin and mucosa. They are adept at presenting antigen. These cells are capable of penetrating beyond intact tight junctions to pick up antigen. Takano's group demonstrated increased numbers of HLA DR CD11c+ dendritic cells in the nasal mucosa of people with allergic rhinitis [46]. Allergic inflammation disrupts these tight junctions [46, 47]. Studies have shown the European dust mite, *Dermatophagoides pteronyssinus* Der p 1, causes disruption of the tight epithelial junctions through its proteolytic activity [48]. Loss of tight junctions allows more allergenic protein to freely pass and penetrate deeper into the tissue. Dendritic cells

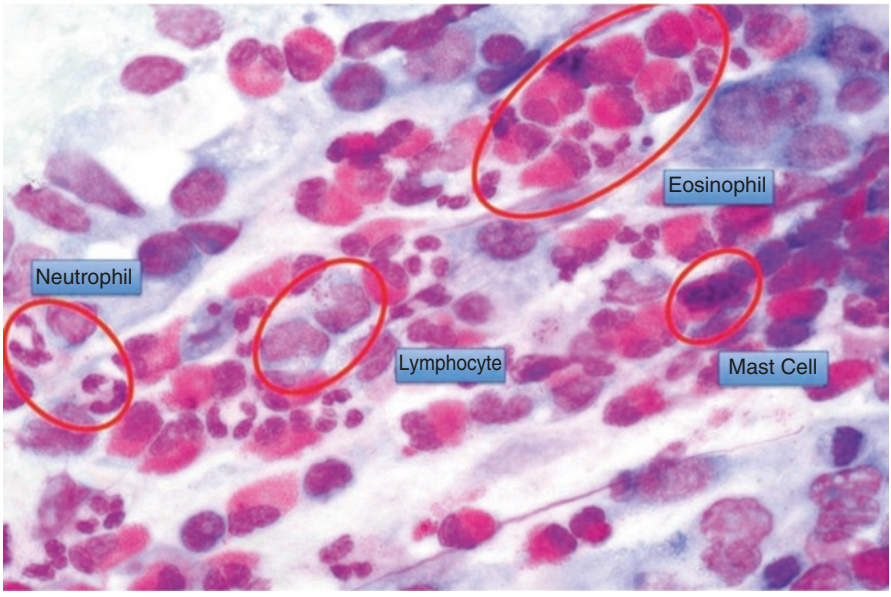


Fig. 17.5 Slide of nasal mucosa in allergic rhinitis. (From Gelardi et al. [64], with permission)

can pick up the antigen through disrupted mucosa and present it to T lymphocytes. The combination of increased dendritic cell numbers and loss of tight junctions promotes allergic inflammation. Epithelial shedding is increased compared to non-allergic controls. Intracellular spaces widen [49] allowing increasing contact and access to antigens. Eosinophils release major basic protein, ECP (eosinophil cationic protein), and eosinophil peroxidase which are cytotoxic to the epithelia. During allergen season, eosinophil numbers increase in the mucosa, and there is increased epithelial shedding [50]. TGFB and TGFB receptors are also increased in damaged epithelia [49]. TGFB disrupts the cell cycle and hinders repair. This contributes to the increased epithelial shedding during this time. Remodeling is further aided by TGFB induction of alpha smooth muscle actin filaments in fibroblasts. These myofibroblasts stimulate collagen deposition. As the numbers of cells increase, so does cytokine release and ongoing inflammation ensue. Over time, remodeling occurs in the nasal mucosa due to release of these inflammatory cytokines.

Eosinophils release cysteinyl leukotrienes (LTC4, LTD4), cationic proteins, eosinophil peroxidase, major basic protein, GM-CSF, IL-4, IL-5, and IL-13 further driving ongoing chronic inflammation and nasal epithelial remodeling [51, 52]. Miadonna's group demonstrated release of LTC4 within 5 minutes after nasal challenge in subjects with grass pollen allergy [53]. Cysteinyl leukotrienes also upregulate adhesion molecule expression on eosinophils surface recruiting more eosinophils and inflammatory cells to the tissue. Eosinophil survival is enhanced due to decreased apoptosis mediated by LTD4. Leukotriene receptor antagonists were studied and demonstrated reduction of eosinophil survival [54]. The role of LTD4 in allergic rhinitis was further characterized. LTD4 plays a significant role in driving nasal congestion. It is 5000 times more potent than histamine [55]. Leukotrienes increase vascular permeability. Vasodilation in the nasal mucosa can increase blood flow by as much as 15% [56]. In addition, EGFR increases in allergic rhinitis. EGFR stimulates mucus hypersecretion [57]. Increased blood flow, vascular permeability, and increased mucus translate to nasal congestion and rhinorrhea and adversely affect airflow and sleep quality.

Histamine also plays a role in regulating the sleep-wake cycle. Histamine is produced in the neurons in the posterior hypothalamus. It acts via H1 receptors and affects arousal, cognition, and memory [58]. Blocking brain H1 receptors disrupts arousal and cognition causing drowsiness and sedation. Older generation antihistamines cross the blood-brain barrier and produce sedation as a side effect. Sedation during times when one is normally awake diminishes the drive to sleep and affects sleep quality. Histamine also stimulates sensory nerves and cough receptors. Coughing also contributes to sleep disruption.

There is a circadian rhythm to mediator release which has been reported. Inflammatory cytokine release increases at night due to decreased cortisol levels [12, 59], thus increasing nasal congestion and obstruction [60, 61]. Severity of symptoms peaks at 6 am [44, 62]. Physiologic relaxation of pharyngeal muscles narrows the oropharyngeal space. Inflammatory mediators increase edema and mucus. The airway narrows further due to the Bernoulli effect. The impact on sleep is therefore due to complex series of interactions, recruitment of inflammatory cells

(eosinophils, basophils, mast cells), and timing of release of inflammatory mediators leading to symptoms. Physical impedance to air movement due to postnasal drainage, edema of the nasal mucosa, and adenotonsillar hypertrophy causes snoring, apnea, hypopnea, and sleep-disordered breathing. Cough triggered by nerve stimulation and mucus drainage further impacts and disrupts sleep.

The pathophysiology of sleep disturbance seen in allergic rhinitis begins at the cellular level. There is a complex interplay between antigen and immune cells mediated by cytokines promoting allergy development. The mucosal architecture is altered leading to macrostructural changes. Physical impedance to air movement occurs. Cough triggered by nerve stimulation, postnasal drainage, mucosal edema, adenotonsillary hypertrophy, and the timing of release of inflammatory mediators all lead to sleep-disordered breathing.

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Sleep-Related Breathing Disorders and Inflammation: TNF-α and IL-6 as Prototypic Examples

18

Leila Kheirandish-Gozal, Hui-Leng Tan, and David Gozal

OSA and Morbidity

Obstructive sleep apnea (OSA) is characterized by repeated events of partial or complete upper airway obstruction during sleep, resulting in disruption of normal ventilation, hypoxemia, and sleep fragmentation, along with increased respiratory efforts and intrathoracic pressure swings aimed at reopening of the occluded or partially occluded upper airway. OSA has major neurocognitive, mood, behavioral, cardiovascular, and metabolic sequelae in both children and adults, and with increasing experience over the last several decades, a large array of additional morbidities has continued to emerge, including erectile dysfunction, ocular conditions, Alzheimer disease, and even cancer in adults and enuresis in children [1–23]. Efforts are ongoing to develop new therapies for OSA based on underlying mechanisms. Currently, the treatment of choice for OSA in children is surgical adenotonsillectomy and in adults consists of the administration of nasal CPAP therapy (continuous positive airway pressure), both of which can give transformative results.

It should be stressed, however, that although OSA is associated with an increased risk of developing a large spectrum of end-organ morbidities, not every patient with OSA will develop evidence of end-organ morbidity. The potential underpinnings of such variable outcomes have been the focus of extensive research activities,

L. Kheirandish-Gozal (✉)
Department of Child Health Research Institute,
University of Missouri School of Medicine, Columbia, MO, USA
e-mail: lgozal@peds.bsd.uchicago.edu

H.-L. Tan
Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, London, UK

D. Gozal
Department of Child Health, University of Missouri School of Medicine, Columbia, MO, USA

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particularly focused around the link between systemic inflammation and specific end-organ morbidities such as neurocognitive, cardiovascular, or metabolic dysfunction [24–29]. However, even though we thoroughly explored the potential contributions of systemic inflammatory pathways, we could not find a distinctive set of plasma-based inflammatory markers that reliably differentiated between those children with and without end-organ-specific risk [13, 30–38]. These problematic results are of further significance considering that many of these morbidities are a silent, potentially reversible evolving process that traditionally will become manifested only years later, i.e., once it reaches an irreversible or only partially reversible stage [39, 40]. Indeed, in a recent meta-analysis, very few if any biomarkers have shown promise in reliably detecting end-organ morbidity associated with OSA [41], reinforcing the need for improved understanding of the mechanisms underlying end-organ morbidity risk in the context of OSA.

Moreover, because the interactions between OSA and obesity are complex, it is difficult to determine independent biomarkers since obesity can influence such biomarkers and vice versa [42–49]. Indeed, obesity is a major risk factor for development of OSA, for complex reasons [50–53]. In general, obese people without OSA have robust upper airway dilator muscle function which prevents pharyngeal collapse during sleep, and how such mechanisms begin to fail in certain patients remains unclear. In addition, treatment of OSA has been associated with worsening obesity [54]. Obesity leads to reduced functional residual capacity, and thus for a given degree of apnea, obese people experience greater desaturations than would their lean counterparts. Finally, some data support the concept that treatment of obese people with OSA is not optimal unless both weight loss and CPAP are provided. To this effect, we will not attempt to disentangle obesity and OSA due to the myriad of reciprocal interactions between these two chronic low-grade inflammatory conditions.

Tumor Necrosis Factor-α

TNF-α is one of the most important cytokines involved in sleep regulation [55–58]. For example, injection of TNF-α induces physiological sleep and increases the time spent in NREM phase. In addition, TNF-α levels follow a circadian variation and are increased after sleep deprivation, and inhibition of TNF-α receptors in the brain is accompanied by the suppression of spontaneous NREM sleep [56]. TNF-α is involved in host defense immune responses and in the pathogenesis of various diseases. TNF-α activates a number of inflammatory pathways mainly via NF-κB, a transcription factor that activates nitric oxide synthase, cyclooxygenase 2, and adenosine A1 receptors, which in turn are implicated in sleep regulation [59–61]. The Krueger laboratory in 1987 [62] first reported on the somnogenic properties of TNF-α. In addition TNF-α was also shown to play a major role in the regulation of normal physiologic sleep in the absence of any immune challenge. Similarly, murine studies in which sleep fragmentation paradigms were implemented mimicking the

disrupted sleep commonly occurring in patients with OSA revealed substantial upregulation of TNF-α in the CNS and other tissues, along with the emergence of increased sleep propensity and cognitive and mood disturbances, even in the absence of sleep deprivation [63, 64]. Furthermore, administration of a TNF-α-neutralizing antibody to wild-type mice exposed to disrupted sleep or similar sleep fragmentation exposures of double TNF-α receptor knockout mice revealed substantial attenuation of the increased sleepiness and cognitive and behavioral disturbances imposed by the sleep fragmentation [63].

It is not surprising that since excessive daytime sleepiness (EDS) is a common manifestation of OSA in adults [65] and in children, particularly when they are obese [66–68], a potential association between EDS and TNF-α would be explored in the context of sleep-disordered breathing [69]. Such assessments have been quite extensive over the last two decades and have overall revealed that circulating TNF-α levels are inconsistently elevated in both adult patients with OSA independent of obesity and in children (see Table 18.1 for a summary of published studies examining TNF-α levels in OSA patients). However, despite such inconsistent findings, a recent meta-analysis has indicated that plasma TNF-α levels are overall increased in OSA, albeit modestly, and are being even proposed as a biological marker of EDS in OSA [70]. Indeed, Nadeem and colleagues reported that standardized pooled mean differences (SPMD) were 1.77 for C-reactive protein (CRP), 1.03 for TNF-α, 2.16 for IL-6, 4.22 for IL-8, 2.93 for ICAM, 1.45 for selectins, and 2.08 for VCAM [70]. In another study in which studies that included pre- and post-CPAP treatment were evaluated in adults, the SPMDs (95% confidence interval [CI]) for CRP, IL-6, IL-8, and TNF-α were 0.452 (95% CI, 0.252–0.651), 0.299 (95% CI, 0.001–0.596), 0.645 (95% CI, 0.362–0.929), and 0.478 (95% CI, 0.219–0.736) in pre- and post-CPAP therapy, respectively, further confirming the pro-inflammatory nature of OSA and the reductions in systemic low-grade inflammation with adherent treatment [71]. Of note, the presence of a single nucleotide polymorphism 308 in the TNF-α gene differs among OSA patients versus controls and is even more likely to be clustered among patients who also manifest EDS [72–77]. To this effect, Vgontzas and colleagues demonstrated that neutralizing TNF-α activity by administration of etanercept was associated with significant reductions in EDS in adult patients with OSA [78]. Taken together, although there is substantial variability from one study to another regarding the presence of elevated systemic concentrations of TNF-α in the context of OSA across the age spectrum, it is likely that in addition to the specific contribution of SDB to increment these levels, there are also a variety of additional confounders that either enhance (e.g., TNF-α polymorphisms) or attenuate (e.g., diet, physical activity) such associations and further provide support to the conceptual framework that the magnitude of systemic inflammation in the context of OSA is a major determinant among several of the morbid consequences of this disease. Future studies specifically examining these relationships and utilizing a composite panel of biomarkers rather than an isolated biomarker may provide improved delineation of personalized risk assessments.

Table 18.1 Brief summary of the published studies on TNF-α levels in adults and children with OSA (italic rows indicate a positive finding and non-italic rows indicate a negative finding)

Reference (authors, year, [ref#])	Number of subjects	Association with	TNF-α levels independently associated with	Effect of treatment (Tx)	Comments	TNF-α levels are increased in OSA Yes/no/ equivocal
Adults						
Jiang et al., 2017 [103]	*120 OSA; 40 controls*	*Carotid atherosclerosis*	*OSA severity cIMT*	*CPAP reduced TNF-α levels*		*Yes*
Heizati et al., 2017 [104]	159 OSA and no-OSA, obese and non-obese	Serum d-lactate Intestinal permeability	No significant associations	No Tx arm		*No*
Fernandez-Julian et al., 2017 [105]	*30 OSA 10 controls*			*Mandibular advancement device reduced TNF-α levels*		*Yes*
Thunstrom et al., 2017 [100]	220 non-sleepy OSA	Coronary artery disease	*No*	Randomization to CPAP or no CPAP for 1 year had no effect on TNF-α levels		*No*
JIn et al., 2017 [106]	*100 OSA 50 controls*	*Atherosclerosis cIMT; pulse wave velocity*	*No*	*CPAP for 3 months reduced TNF-α levels*		*Yes*
Binar et al., 2017 [107]	28 OSA on CPAP 29 OSA undergoing upper airway surgery		*No*	No effects of either Tx on TNF-α levels		*No*
Mutlu et al., 2017 [108]	*25 OSA undergoing uvulopalatal flap (UPF) surgery*		*No*	*UPF surgery reduced TNF-α levels*		*Yes*

Li et al., 2017 [109]	*Meta-analysis of 2857 OSA and 2115 controls*	*OSA severity*	*Yes; in mild, mild-to-moderate, moderate, moderate-to-severe and severe OSAS, circulating TNF-alpha was higher than controls by 0.99, 1.48. 7.79, 10.08, and 8.85 pg/mL, with significant heterogeneity (I2: 91.2%, 74.5%, 97.6%, 99.0%, and 98.1%)*	*No Tx*		*Yes*
Hirotsu et al., 2017 [110]	*1042 subjects from community*	*OSA severity Metabolic syndrome*	*Positive association in women and negative in men*	*No Tx*		*Yes*
Vicente et al., 2016 [111]	89 OSA; 28 snorers; 26 controls	Pharyngeal lavage and plasma	Higher cytokines including TNF-α in pharyngeal lavage but not in plasma	1-year follow-up CPAP – Improvements in TNF-α in pharyngeal lavage		Equivocal
De Santis et al., 2015 [112]	*20 obese OSA 6 non-obese OSA*			*Reduced cytokines after 6 months of CPAP or surgery*		*Yes*
Leon Cabrera et al., 2015 [113]	*52 subjects (10 controls, 42 obese OSA)*	*Insulin resistance*	*Higher TNF-α*	*No Tx*	*Inverse relationship between IL-10, but not TNF-α and insulin resistance*	*Yes*
Stradling et al., 2015 [114]	391 OSA		No differences before and after treatment	CPAP for 6 months		*No*
Bouloukaki et al., 2014	*31 OSA and erectile dysfunction (ED) 15 OSA and no ED*		*Higher TNF-α plasma levels when ED present*			*Yes*

(continued)

Table 18.1 (continued)

Reference (authors, year, [ref#])	Number of subjects	Association with	TNF-α levels independently associated with	Effect of treatment (Tx)	Comments	TNF-α levels are increased in OSA Yes/no/ equivocal
Salord et al., 2014 [115]	52 OSA and no-OSA obese	Metabolic syndrome	No differences in OSA with or without metabolic syndrome			*No*
Ciccone et al., 2014 [116]	*80 OSA 40 controls*	*cIMT*	*Higher TNF-α plasma levels associated with higher cIMT*	*No Tx*		*Yes*
Yoshikawa et al., 2014 [117]	*22 OSA*	*Association with apnea-hypopnea index*	*Higher TNF-α plasma levels*	*CPAP for 3 months reduced TNF-α plasma levels*		*Yes*
Karamanli et al., 2014 [118]	35 OSA			CPAP for 3 months – no changes in TNF-α plasma levels		*No*
Matos et al., 2013 [119]	*363 men*	*ED*	*Higher TNF-α plasma levels when ED and OSA present*	*No Tx*		*Yes*
Aihara et al., 2013 [120]	43 OSA	Serum and induced sputum	Sputum TNF-α levels, but not serum levels, correlated with OSA severity	No Tx		*No*
Qian et al., 2012 [121]	70 severe OSA	Hypertension	Higher TNF-α plasma levels associated with hypertension	No Tx		Equivocal
Oyama et al., 2012 [122]	*32 OSA and metabolic syndrome*	*Endothelial function*		*CPAP for 3 months reduced TNF-α plasma levels*		*Yes*
Svensson et al., 2012 [123]	*230 habitually snoring women and 170 controls*	*AHI ODI3%*	*Significant association between TNF-α levels and ODI3%*			*Yes*
Hegglin et al., 2012 [124]	*66 OSA*			*CPAP 8 months reduced TNF-α plasma levels in men but not in women*		*Yes*

Eun et al., 2010 [125]	*51 OSA*	*EDS*		*Upper airway surgery with 4-week follow-up showed significant reductions in TNF-α plasma levels and EDS*		*Yes*
Li et al., 2010 [126]	*OSA (n = 113) Hypertensive without OSA (n = 73) Hypertensive with OSA (n = 134) Controls (n = 97)*		*OSA patients have higher TNF-α levels*	*No Tx arm*		*Yes*
Sahlman et al., 2010 [127]	*84 mild OSA 40 controls*		*OSA patients have higher TNF-α levels*	*No Tx arm*		*Yes*
Tamaki et al., 2009 [128]	*33 OSA 13 controls*	*Monocyte production of TNF-α levels*	*Circulating monocytes in OSA patients have higher TNF-α levels*	*No Tx arm*		*Yes*
Constantinidis et al., 2008 [129]	*24 OSA 12 non-obese and 15 obese controls*			*Surgery decreased monocyte TNF-α production*		
Minoguchi et al., 2004 [130]	*24 OSA 27 controls*			*CPAP for 1 month decreased monocyte production of TNF-α*		
Steiropoulos et al., 2009 [131]	*52 OSA*			*CPAP for 6 months (n = 32 with good adherence and 20 nonadherent). Good adherence reduced TNF-α plasma levels*		*Yes*

(continued)

Table 18.1 (continued)

Reference (authors, year, [ref#])	Number of subjects	Association with	TNF-α levels independently associated with	Effect of treatment (Tx)	Comments	TNF-α levels are increased in OSA Yes/no/ equivocal
Dorkova et al., 2008 [132]	*32 severe OSA and metabolic syndrome*			*CPAP adherence for 8 weeks (n = 16) reduced TNF-α plasma levels but no changes if nonadherent (<4 h/night)*		*Yes*
Kanbay et al., 2008 [133]	*106 OSA 32 controls*		*OSA patients, particularly if concurrent obesity, have higher TNF-α levels*	*No Tx arm*		*Yes*
Bravo et al., 2007 [134]	*50 OSA 20 controls*	*EDS*	*OSA have higher TNF-α levels unrelated to EDS*	*No Tx arm*		*Yes*
Kataoka et al., 2004 [135]	*27 OSA 11 controls*		*Higher TNF-α levels in OSA*	*No Tx arm*		*Yes*
Ciftci et al., 2004 [136]	*43 OSA 22 controls*	*BMI*	*OSA have higher TNF-α levels unrelated to BMI*	*No Tx arm*		*Yes*
Imagawa et al., 2004 [137]	110 OSA 45 controls		No differences in TNF-α levels	No Tx arm		*No*
Alberti et al., 2003 [138]	*18 OSA 20 controls*		*OSA have higher TNF-α levels*	*No Tx arm*		*Yes*
Children						
Kontos et al., 2017 [139]	*19 children*	*Cardiac magnetic resonance imaging (aortic blood flow velocity and left and right ventricular systolic function)*	–	*No Tx arm*	*Intracellular TNF-α in CD8+T cells*	*Yes*

Van Eyck et al., 2017 [93]	164 overweight and obese children (111 controls, 28 mild OSA, 25 moderate-to-severe OSA)	OSA severity	None	No Tx arm		*No*
Smith et al., 2017 [94]	90 controls 65 OSA	Pulse transit time (PTT)	Shorter PTT	No Tx arm		*No*
Huang et al., 2016 [95]	47 non-obese OSA 32 controls	Cognitive function	Association with general cognitive function	No Tx arm		Equivocal
Gaines et al., 2016 [96]	392 adolescents with no OSA, mild, moderate, and severe OSA	Visceral adipose tissue	None	No Tx arm		*No*
Mutlu et al., 2014 [140]	*35 children OSA*	*None*	*None*	*T&A reduced TNF-α at 6-month follow-up*		*Yes*
Alexopoulos et al., 2013 [141]	24 moderate-to-severe OSA 22 mild OSA 22 controls	EDS	No differences in TNF-α across 3 groups; no association with EDS			*No*
Chu and Li, 2013 [142]	90 obese children with OSA			T&A and 6-month follow-up showed no changes in TNF-α or IL-6		*No*
Gozal et al., 2010 [143]	*298 snoring children*	*EDS*	*TNF-α significantly higher with more severe OSA and when EDS present*	*T&A and 3-month follow-up showed significant reductions in TNF-α*		*Yes*
Li et al., 2008 [144]	142 snoring children		TNF-α not higher in OSA but IL-6 and IL-8 elevated	No Tx arm		Equivocal

Abbreviations: *cIMT* carotid intima media thickness, *CPAP* continuous positive airway pressure, *MAD* mandibular advancement device, *Tx* treatment, *T&A* adenotonsillectomy, *EDS* excessive daytime sleepiness, *ODI3%* oxygen desaturation index 3%

Interleukin 6

Interleukin 6 (IL-6) belongs to the so-called IL-6 family of cytokines. All of its members, which include cardiotrophin-1, oncostatin M, leukemia inhibitory factor, cardiotrophin-like cytokine, ciliary neurotrophic factor, and interleukins 11, 27, 30, and 31, bind to the glycoprotein 130 (gp130) as a β-receptor to activate intracellular signaling cascades in which the signaling complexes generally consist of homo- or heterodimers of gp130 in combination with other cytokine receptors [79]. Plasma levels of the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP) predict, in addition to other disease conditions such as diabetes and cognitive function deterioration, the risk of vascular disease. We and others have conducted extensive work showing that overall hsCRP levels tend to be elevated in children with OSA, independent of the degree of obesity [25]. IL-6 synthesis is immediately upstream of hsCRP and regulates its synthesis in the liver, but visceral adipose tissues are also a major source of inflammatory mediators, including IL-6. Adipose tissue inflammation is induced by intermittent hypoxia and by chronic sleep fragmentation [55, 80–86], and may cross talk with endothelial cells via adipocyte-derived mediators such as IL-6, and promote NF-κB-dependent endothelial dysfunction [87].

Accordingly, it is not surprising that IL-6 plasma levels have been shown to correlate with endothelial dysfunction, arterial stiffness, and extent of subclinical atherosclerosis and are similarly predictive of incident type 2 diabetes and obesity [88, 89]. In this regard, the close analogy between the list of diseases in which IL-6 may serve as either a biomarker of risk or an actual mediator of morbidity, and the repertoire of morbid consequences associated with OSA, prompted the hypothesis that IL-6 may serve as a reliable indicator of either the presence of OSA or provide risk estimates of OSA-associated morbidities. In support of this assumption, a recent study has demonstrated that intermittent hypoxia, one of the hallmark characteristics of OSA, induces the polarization of macrophages to a pro-inflammatory phenotype, along with increased production of IL-6 [90]. In a study that recruited obese patients with and without OSA, biopsies of adipose tissue and plasma levels revealed substantial increases in the expression and levels of a variety of pro-inflammatory cytokines, including IL-6, and such changes were markedly reduced upon administration of CPAP therapy for 6 months [91]. Interestingly, adult patients with OSA and objective EDS documented by lower multiple sleep latency test (MSLT) showed significantly elevated daytime and nighttime IL-6 levels, which were not present when subjective EDS was used as the indicator of sleepiness [92]. A study in which eight published reports in adults were pooled for IL-6 findings indicated that the means of plasma levels of IL-6 ranged from 1.2 to 131.66 pg/ml before CPAP treatment and between 0.45 and 66.04 pg/ml after CPAP treatment ($p < 0.05$), but that there was significant heterogeneity in this endpoint (df = 7, $p < 0.00001$, I(2) = 95%) [93].

When exploring whether OSA is also associated with increased IL-6 levels in children, similar and relatively prominent heterogeneity of findings was also reported, as shown in relation to TNF-α levels above [94–97]. It is very likely that a large component of such heterogeneity may reside in the genetic variance for both

IL-6 and CRP genes that exist among different populations [98]. In a recent meta-analysis of both gene polymorphisms for IL-6 and plasma levels of this cytokine, the authors concluded that IL-6 gene polymorphism −174 G/C, but not polymorphism −572 G/C, is associated with OSA risk in adults, and that IL-6 levels are overall increased in OSA, but CPAP treatment does not consistently reduce elevated IL-6 levels [99], possibly due to the concurrent presence of obesity and cardiovascular or metabolic disease [100, 101]. In children with OSA, IL-6 levels were also generally increased and T&A surgery significantly decreased IL-6 levels [99].

Conclusions

Using two classic prototypic inflammatory mediators such as IL-6 and TNF-α as reporters of the pro-inflammatory milieu elicited by the presence of OSA, it is the overall consensus that the presence of OSA in both adults and children can be viewed as a persistently low-intensity inflammatory disease and that such inflammatory processes are heterogeneous and clearly may be modulated by both genetics, environment and lifestyle. Notwithstanding, the data are congruent with the assumption that the finding of elevated inflammatory markers likely signifies the underlying presence of end-organ morbidity. Future studies aimed at unraveling reliable and specific biomarker panels that can discern with confidence who are the patients at higher risk for OSA-induced morbidities should enable not only improved understanding of such morbidities but also implement the goal of personalized medicine among OSA patients [102, 103].

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Circadian Rhythm of Allergic Rhinitis, Skin Testing and Allergen Immunotherapy

19

Arjola Cosper, John Oppenheimer, and Linda Cox

Allergic Rhinitis

Clinical Symptoms

Allergic rhinitis (AR) follows a 24-h diurnal pattern of variation in symptoms [1, 2]. A study by Reinberg et al. recruited 765 patients with AR and followed them for over an 11-month period. Participants self-assessed severity of symptoms such as sneezing, rhinorrhea, obstruction, pruritus of the eyes and nose, cough and/or wheezing four times daily over 1-week period via visual analogue scales as illustrated in Fig. 19.1 [3]. Overall, symptoms were reported to be the most severe in the morning with a mild peak in early evening [3]. In addition, circannual changes in allergic reactivity were noted.

The mechanism for time of day differences in allergic rhinitis is complex but likely relates to both timing of pollen release and endogenous rhythms (i.e. variations in endogenous hormones, corticosteroids, etc). Specifically, ambient pollen counts are highest in the morning and likely contribute to the uptick in morning symptoms. With regard to endogenous rhythms, increased susceptibility to AM symptoms occurs because of (1) endogenous nasal cycling, which is the alternating partial congestion and decongestion of the nasal turbinates due to selective activation of one half of the autonomic nervous system by the hypothalamas.

A. Cosper (✉) · J. Oppenheimer
Department of Medicine, University of Miami at Holy Cross Hospital, Fort Lauderdale, FL, USA

L. Cox
Department of Medicine, University of Miami at Holy Cross Hospital, Fort Lauderdale, FL, USA

University of Wyoming Medical Center, Casper, WY, USA

Nova Southwestern University, Department of Medicine and Dermatology, Fort Lauderdale, FL, USA

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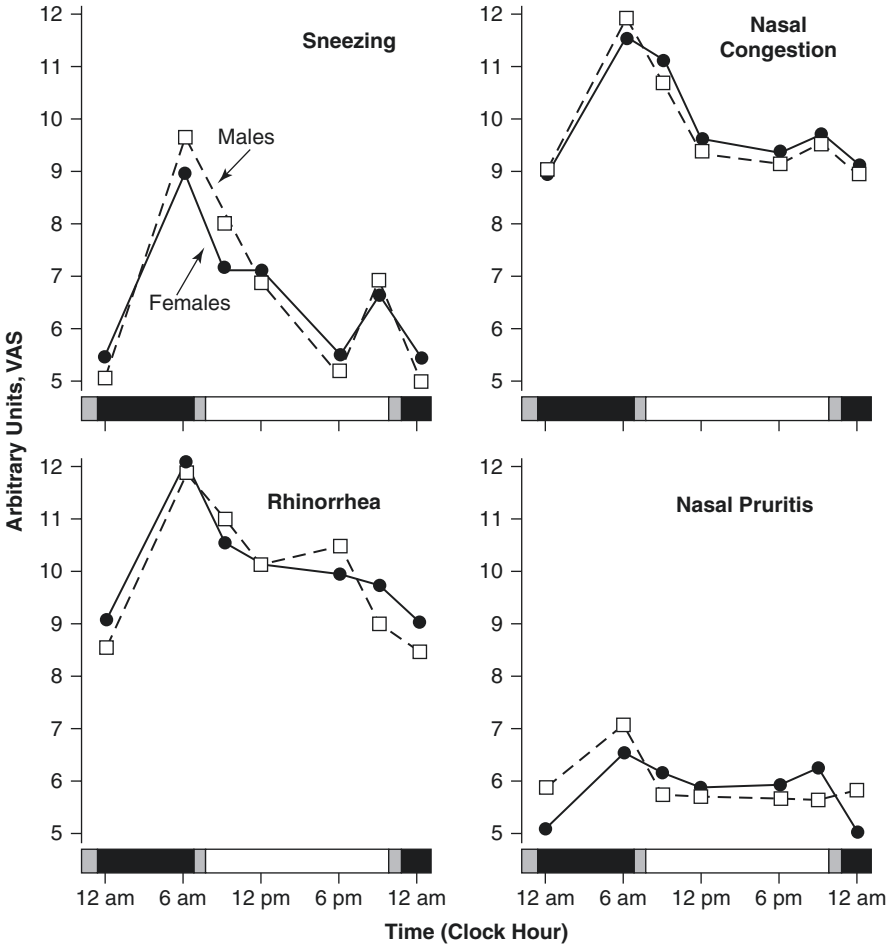


Fig. 19.1 Diurnal variation in AR symptoms—Sneezing, nasal congestion and rhinorrhea were more problematic than nasal pruritus. On average, the severity of all the symptoms was greatest in the morning. Open and shaded portions of the time axis indicate the clock time of activity and sleep of subjects. (From Smolensky et al. [1], with permission)

Endogenous nasal cycling is a 'normal' phenomenom which should not be confused with pathological nasal congestion, (2) increase susceptibility to inflammatory response and (3) supine position during sleep [4]. Responsiveness of nasal mucosa to methacholine challenge is increased at 6 AM as compared to 3 PM [5]. These changes might be controlled by circadian clock gene rhythms [6].

Inflammation AR

The inflammatory response of AR has been studied and categorized into early and late phases. The early phase response is the immediate response after IgE-sensitized

cells have encountered the allergen: following which, release of histamine, prostaglandins and cytokines results from degranulated mast cells. This phase is associated with the symptoms of sneezing, pruritus, rhinorrhea and congestion. The late phase response is more commonly associated with congestion. It generally occurs a few hours after allergen exposure and involves a cellular response including infiltration of leukocytes, T-cells and eosinophils [7].

As mentioned above, Aoyagi et al. compared a group of eight healthy children to eight children with AR aged between 9 and 14, exposing them to methacholine nasal challenge and collected nasal secretions at both 6 AM and 3 PM. They found that the volume of nasal secretions collected after the 6 AM challenge was significantly greater than the 3 PM one, as were the number of inflammatory mediators such as histamine, tryptase and eosinophilic cationic protein [8]. Their results demonstrate that nasal reactivity variation is related to activation of eosinophils and basophilic cells in the nasal mucosa, and this could explain the diurnal symptomatic variation in AR.

Fidan and colleagues attempted to determine the mechanism for these changes in inflammatory cells by measuring levels of cortisol and melatonin in 35 recently diagnosed AR patients compared to 24 healthy controls (age and sex matched). The authors found that there was a circadian pattern in salivary melatonin and cortisol levels with an overall decrease in both hormones in patients with AR compared to healthy subjects [9]. This may explain the diurnal patern of AR symptoms as lower levels of cortisol in AR patients impair suppression of chronic inflammation in the nasal mucosa. This is probably the reason why intranasal steroids are the most effective single agent for AR and commonly the first-line therapy for most patients suffering from AR. Interestingly, in a recent study performed in mice, intranasal steroids caused a time shift in the clock gene product (PER2) resetting the circadian clock in the nasal mucosa [10].

Although more work is needed on optimal timing on therapy to minimize symptoms, several studies on long-acting, non-sedating antihistamines suggest time of administration does not have a significantly different impact on rhinitis symptoms [11, 12]. Although not clearly studied in allergic rhinitis, findings from asthma suggest higher efficacy of nocturnal dosing of steroids and leukotriene receptor antagonists [13]. This is likely related to maximal efficacy during the time of greatest need (when endogenous steroids are at their lowest) [14]. Chronotherapy (time-based treatment) for allergic rhinitis is an area in need of further exploration.

Skin Testing

When considering chronobiology and allergic disease, beyond the lung and nose, a similar response is seen in the skin as manifested by change in skin test response. Variability in skin test size was first reported by Reinberg and colleagues in the 1960s, when they demonstrated that skin reactivity to histamine, a direct stimulus, and the indirect mast cell secretagogue compound 48/80 demonstrated maximal response between 7 PM and 11 PM with a nadir at 7 AM. The authors postulated that the variability in skin test response was the same in both the direct skin stimuli (histamine) and indirect stimuli (compound 48/80) likely as the result of skin

responsiveness versus fluctuation in the release of mast cell mediators [15]. Lee and colleagues extended these results in their study finding a similar nadir in skin test responsiveness first thing in the morning, in this case demonstrating the same findings with allergens (grass as well as house dust extracts) [16]. In the discussion of their paper, Lee warns that potential false-negative response in skin testing could occur if testing was performed early in the morning. In 1989, Vichyanond and Nelson performed a more robust evaluation of this issue. In their study, they examined 20 adults and 20 children with significant skin prick test positivity to short ragweed extract. In an effort to carefully assess a potential change in skin test size, they performed testing at 8 AM and 4 PM and relied upon use of fivefold serial dilutions [17]. Similar testing was also performed to histamine. For greater accuracy, areas of both wheals and flares were measured by computer planimetry, and to mimic real-world testing, conventional skin test measurement was also performed. As opposed to previous studies, in this study, the authors found that there was a trend for the morning mean skin test size to be larger than evening test results for both ragweed and histamine. This difference was only significant for ragweed ($p = 0.03$) when using the planimetry measure, while conventional skin test scoring demonstrated similar findings ($p = 0.3$ for ragweed and $p < 0.05$ for histamine). Therefore, these differences were quite small and not significant enough to influence the timing when skin testing is performed in a clinical setting. This is the reason that despite small diurnal variability in skin test responses, there is no need to perform skin testing at certain times of day.

Beyond circadian variability in allergic disease, there may also be a circannual variability (i.e. seasonal variations). A study by Oppenheimer and Nelson explored this issue by performing skin testing with fivefold serial dilutions to a specific pollen during its season (ragweed), a specific pollen from an earlier season (tree), a perennial allergen (dust mite or cat) and histamine control during the projected trough of ragweed-specific IgE, at the peak of ragweed pollen count, the estimated peak of ragweed-specific IgE and a time of no pollen exposure, in a group of 30 subjects with both symptoms during ragweed season and a positive skin test to this allergen. They found that reactions during the peak of IgE to ragweed were greatest for both seasonal allergens (ragweed and tree) as well as to histamine [18]. The authors speculate that this increase in skin test responsiveness may represent a priming effect on the skin secondary to seasonal pollen exposure or could represent a circannual rhythm unrelated to pollen exposure. Interestingly, some postulate a circannual rhythm to be the cause of asthma exacerbations in October and November [19]. However, this level of variability was not clinically significant but does highlight the potential for further irregularity in response beyond circadian variability.

Overall, results in skin test variability are like that of the nose, with greatest sensitivity seen first thing in the morning compared to the early evening. Although not well studied, one could easily postulate that this is likely the effect of circadian variability of the inflammatory milieu. Similar response seen both in the skin and lung should not be surprising given that circadian variability in inflammatory mediators would be expected to have an analogous effect in different end organs.

Allergen Immunotherapy

Despite the long history of subcutaneous allergen immunotherapy ("allergy shots") in the field of allergy and the risk of reactions, a recent paper by Bavishi and Fishbein was the first to publish on time of day differences in reactions. Specifically they found increased cutaneous reactions with PM dosing, but no time of day difference in likelihood of anaphylactic reactions. Injections after 3 PM had a cutaneous reaction rate (including small local reactions) of about 3.5%, as compared to other times of day which were around 2–2.5%. The adjusted odds of having a reaction with PM injection was 1.43 (1.20–1.70) as compared to AM injection [20]. Previous work on this topic was noted in one abstract and clinical anecdotes, suggesting no rhythm to anaphylaxis, but cutaneous reactions had not been evaluated [21, 22]. It is possible that this diurnal variation in allergy immunotherapy injection reaction was due to greater exposure to the aeroallergen in the PM vs AM, because the AR patient may have implemented indoor enviromental controls that can reduce indoor and outdoor allergen. Thus, their allergen 'load' in the AM could be considerably less than the PM, after they have spent time outside and in indoor environments without such allergen avoidance measure. This would be similar to the seasonal 'priming' effect discussed above.

Clinically, patients with frequent cutaneous reactions to "allergy shots" should consider switching their injection schedule to receive shots in the morning. The implications of timing of allergen immunotherapy with other modes of administration (sublingual, oral, epicutaneous, etc.) are an area in need of further study. The potential to improve tolerance or efficacy of allergen immunotherapy depending on time of day of administration is an area in need of further exploration as well.

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20 Differentiating Upper Airways Resistance in Adenoid Hypertrophy, Allergic Rhinitis, and Obstructive Sleep Apnea: Imaging and Approaches

Sophie Shay and James W. Schroeder Jr.

Upper airway resistance represents a multilevel condition which can be affected from conditions in the nasal cavities, nasopharynx, oropharynx, or larynx. Upper airway resistance syndrome (UARS) was initially coined by Guilleminault et al. in 1993 to describe adults with symptoms of sleep-disordered breathing with associated measures of increased airway resistance [1]. Pediatric UARS is characterized by abnormal breathing patterns and increased respiratory effort during sleep, without apneas, hypopneas, or drops in oxygen saturations [2]. In children, UARS may be hard to diagnose as the symptoms present differently during stages of growth.

Clinical symptoms and presentations vary among infants, toddlers, prepubescent children, and teenagers. Infants can present with upper airway resistance during an "apparent life-threatening event" (ALTE), of which 50% may be represented by abnormal breathing during sleep. [3, 4] In toddlers, nocturnal symptoms of sleep-disordered breathing will be more obvious, with restless sleep, snoring, apneas, hypopneas, and daytime hyperactivity. These young children may also present with recurrent earaches, upper respiratory infections, and obligate mouth breathing. Prepubescent children will also present with classic symptoms of sleep disordered breathing, such as enuresis, restless sleep, and difficulty in school. Finally, teenagers are more likely to report difficulty waking in the morning, daytime fatigue, anxiety, and postnasal drip.

S. Shay (✉)
Division of Otolaryngology-Head and Neck Surgery, Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern McGaw Medical Center, Chicago, IL, USA
e-mail: SShay@luriechildrens.org

J. W. Schroeder Jr.
Department of Surgery, Division of Otorhinolaryngology, Head and Neck Surgery, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Department of Otorhinolaryngology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

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In adults, UARS is related to an abnormal breathing pattern during sleep resulting in daytime hypersomnolence [1]. Specifically, these patients demonstrate frequent wakenings lasting as short as 3 seconds leading to sleep fragmentation. The most common symptoms are excessive daytime sleepiness, fatigue, and fragmented sleep. It is thought that these transient arousals are related to increased respiratory effort during sleep coinciding with a reduction in tidal volume. On polysomnogram, upper airway resistance is usually seen with flow limitation during respiration. The definition of UARS in adults has varied over the last 20 years, with no clear definitions based on polysomnogram findings. Some authors have considered it on a spectrum between primary snoring and obstructive sleep apnea (OSA), with some authors believing it is a subgroup of OSA based on similar symptomology and pathophysiology. Conversely, there are others who consider it a diagnosis distinct from OSA, with potential differences in sleep EEG findings. Treatment of UARS in adults is similar to the management of OSA, which is described elsewhere in this text. [5]

Adenoid Hypertrophy

The adenoid is an organ composed of lymphoepithelial tissue within Waldeyer's ring which sits at the posterosuperior nasopharynx and plays a role in the immune system of the upper aerodigestive tract. Adenoid hypertrophy (Fig. 20.1) is one of the most common conditions in the pediatric population and has been associated with snoring, nasal airway obstruction, sleep apnea, and recurrent otitis media.



Fig. 20.1 Nasal endoscopy view of adenoid hypertrophy with complete obstruction of the nasopharynx. The adenoid is labeled accordingly; "S.P." denotes the soft palate

[6–10] Clinically significant adenoid hypertrophy is rare among adults and not a typical level of airway obstruction. Among children, adenoid hypertrophy is thought to be a predisposing factor to abnormal craniofacial development, commonly referred to as "adenoid faces," with a narrow maxilla, posterior crossbite, increased anterior face height, and retrognathic mandible [11–14]. Adenoidectomy is one of the most frequently performed surgeries for children in the United States, with obstruction as a more prominent indication for surgery than infection [7, 15].

The diagnosis of adenoid hypertrophy can present a challenge to the clinician. Multiple modalities have been suggested to study and quantify the degree to which adenoid tissue obstructs the nasopharyngeal airway. However, there are currently no published, age-specific guidelines to guide clinicians in diagnosing adenoid hypertrophy. The most common diagnostic modalities used in clinical practice are lateral neck radiographs and nasal endoscopy [6, 7]. However, there is little consensus on the grading of adenoid size even with previously described methods. Additionally, the significance of adenoid hypertrophy varies with age, as the adenoid hypertrophy is rarely found in children under 1 year of age, while the adenoid grows rapidly between 3 and 5 years of age [16]. The Nasal Obstruction Index (NOI) is a clinical screening assessment validated by Paradise and colleagues [17] which scores the degree of mouth breathing and hyponasality and can reliably rule out adenoid hypertrophy when clinical assessment suggests no presence of obstruction. However, as Marchisio and colleagues [18] and Torretta and colleagues [19] concluded, the NOI does not correlate well with endoscopic findings and has limited utility in diagnosing adenoid hypertrophy. Alternative diagnoses for upper airway resistance, such as allergic rhinitis, should be considered for patients with high NOI scores or clinical symptoms without concurrent adenoid hypertrophy on further workup.

Allergic Rhinitis

Allergic rhinitis is a common cause of anterior nasal obstruction in both adults and children, while adenoid hypertrophy is a common cited source of posterior nasal obstruction in children. Allergic rhinitis is widely prevalent among the pediatric population, with an incidence cited as high as 40%, and is the most common chronic allergic condition among children [20–22]. Allergic rhinitis is typically categorized as seasonal versus perennial depending on allergic triggers and may also be classified as intermittent versus persistent depending on the duration of symptomology [22]. Otitis media with effusion, sinusitis, asthma, and sleep-disordered breathing are considered physical complications of pediatric allergic rhinitis. Children with allergic rhinitis may also have poor school performance, difficulties with sleep, and daytime hyperactivity, making the manifestations of allergic rhinitis difficult to distinguish from those of sleep-disordered breathing [21].

The mainstay of diagnosing allergic rhinitis is a comprehensive history and physical, starting first with a high index of suspicion for allergic rhinitis in the pediatric population [23]. Symptoms of allergic rhinitis typically include clear rhinorrhea, nasal congestion, sneezing, and nasal itching [24]. Nasal congestion may be

bilateral, unilateral, or alternating and generally worsens at night. Patients or parents may report frequent sniffing, snorting, nose blowing, or throat clearing, as well intermittent epistaxis, and reduced sense of smell or taste. Taking into the account the association with systemic allergic disease, patients might also report itchy, watery eyes, or eczematous rashes. Symptoms of allergic rhinitis may be confounded with sleep-disordered breathing due to sleep disturbances from congestion. Chronic allergic rhinitis may lead to abnormal midface development, chronic mouth breathing, and dental malocclusion – findings which may also be attributed to adenoid hypertrophy. Mucosal edema in the paranasal sinuses and Eustachian tube may also cause facial pain and pressure as well as ear fullness. In severe, chronic cases of allergic rhinitis, patients may also report hypernasal speech, poor appetite, poor growth, and fatigue.

On physical exam, children with allergic rhinitis may present with an allergic nasal crease – a horizontal crease or fold across the nasal dorsum along the lower third of the nose caused by an "allergic salute," which is the repetitive upward rubbing of the nose with the palm of the hand. Children may also have "allergic shiners," with darkening and edema of infraorbital skin. Findings of allergic conjunctivitis – tearing, conjunctival edema, and hyperemia – may also be present on physical examination. On anterior rhinoscopy, nasal mucosa has an edematous, boggy/bluish appearance without significant erythema, and the nasal cavities may have thin, clear nasal secretions. The inferior turbinates may be hypertrophied, obstructing the nasal cavity (Fig. 20.2). Examination of the nasal cavity may be augmented with the use of the otoscope with a nasal adapter, nasal speculum, or indirect mirror for nasopharyngeal examination [23].

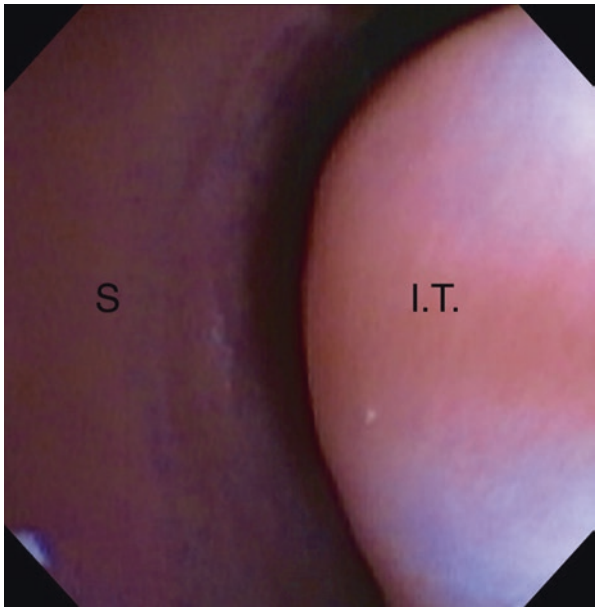


Fig. 20.2 Endoscopic anterior rhinoscopy of the left nasal cavity, showing inferior turbinate hypertrophy filling the anterior nasal cavity. "I.T." denotes the inferior turbinate; "S" denotes the nasal septum

The diagnosis allergic rhinitis should be considered an organ-specific disease under the spectrum of systemic allergic disease. In fact, allergic rhinitis may predispose patients to lymphoid hypertrophy, particularly adenotonsillar hypertrophy from chronic postnasal drip, and inflammation of the nose and pharynx. As such, while adenoid hypertrophy, allergic rhinitis, and even obstructive sleep apnea may present as distinct disease processes, in some patients, they may represent manifestations of an allergic disease spectrum. In a prospective study on 315 patients with adenoid hypertrophy and allergic rhinitis with age-matched controls with only a diagnosis of allergic rhinitis, Huang and Giannoni [25] found that patients with both allergic rhinitis and adenoid hypertrophy had increased skin reactivity to mold allergens. Modrzynski and Zawisza [26] used acoustic rhinometry and nasal endoscopy to assess adenoid hypertrophy following birch tree pollination period and reported a resulting decrease in nasal cavity volume and increase in adenoid size on endoscopy. On the contrary, among 205 children, Ameli and colleagues [27] compared measurements of anterior nasal obstruction with grading of adenoid hypertrophy and found a statistically significant negative correlation between degree of anterior nasal obstruction and adenoid hypertrophy ($r = -0.41$, $p < 0.001$), suggesting an inverse relationship between the two. In this same study, probability of decreased adenoid volume was associated with increased anterior nasal obstruction and with patients with a history of allergy.

Obstructive Sleep Apnea

Sleep-disordered breathing represents a continuum of abnormal breathing patterns during sleep, ranging from mild snoring to upper airway resistance syndrome to obstructive sleep apnea (OSA), which is defined by an abnormal polysomnogram with noted obstructive events [28]. Upper airway resistance syndrome is defined as repetitive respiratory effort-related arousals with similar daytime symptoms and cardiovascular effects as OSA [2, 29]. The prevalence of pediatric OSA has been reported between 0% and 5.7% [28]. Nighttime symptoms of sleep-disordered breathing include snoring, mouth breathing during sleep, and witnessed pauses in breathing. Additionally, parents may report excessive daytime sleepiness, daytime hyperactivities, difficulty in school, and, when at an extreme, social withdrawal and aggression. Physical manifestations of OSA include poor growth, systemic hypertension, pulmonary hypertension, and cor pulmonale [30]. The Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) 2011 clinical practice guidelines recommended that children with complex medical conditions (obesity, Down syndrome, craniofacial abnormalities, neuromuscular disorders, sickle cell disease, or mucopolysaccharidoses) and discordant physical exam findings should undergo preoperative polysomnography [31].

Allergic rhinitis is a known risk factor for obstructive sleep apnea as a precursor to lymphoid hyperplasia [32]. Adenotonsillar hypertrophy is well established as a cause of sleep-disordered breathing and OSA (Fig. 20.3). Adenoidectomy or adenotonsillectomy is considered an effective, first-line surgical therapy for

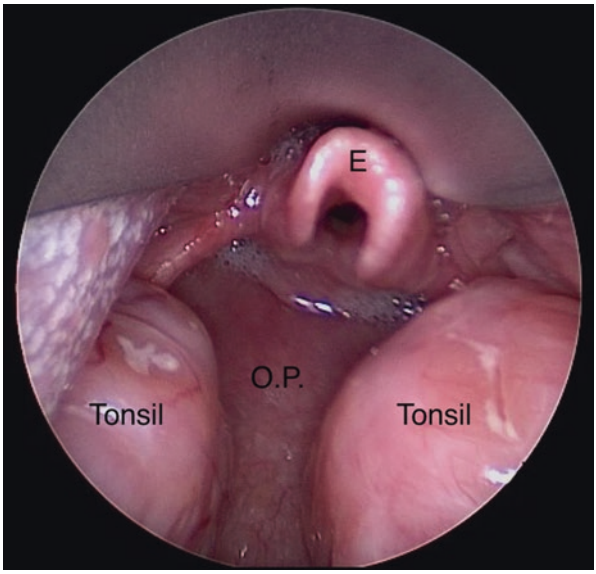


Fig. 20.3 Microdirect laryngoscopy view of tonsillar hypertrophy with severe crowding of the oropharynx and supraglottic airway. Tonsils are labeled accordingly, "E" denotes the epiglottis, and "O.P." denotes the oropharynx

sleep-disordered breathing and OSA in children and has been found to be 90% curative [28, 33].

Unfortunately, patient and parental history is not specific for OSA and may overall be suggestive of only sleep-disordered breathing [34, 35]. Videotaped sleep, nocturnal pulse oximetry, and nap polysomnography may be alternatives in diagnosing OSA. However, these aforementioned techniques tend to be unreliable and have a low negative predictive value of OSA compared to lab-based polysomnography, which is considered the gold standard of diagnosing OSA [28, 31]. Additionally, these methods are inferior to lab-based polysomnography in assessing the severity of OSA.

Diagnostic Tests

Radiographic Assessment

Lateral neck films (Fig. 20.4) are commonly used to assess adenoid size and can be obtained by pediatricians, family practitioners, and dentists in the evaluation of adenoid hypertrophy. It is a sagittal X-ray of the head and neck which is readily available, low cost, and generally reproducible [7]. Kolo and colleagues found high inter-rater reliability in sizing of adenoid tissue between radiologists and otolaryngologists [36]. Limitations of lateral neck films include exposure to radiation, patient cooperation, anatomic differences based on neck rotation, and dynamic changes with respiration using a non-dynamic modality. Given the limitations in assessment of dynamic, three-dimensional assessment of adenoid size, lateral radiographic assessment for adenoid hypertrophy tends to be most useful as a screening

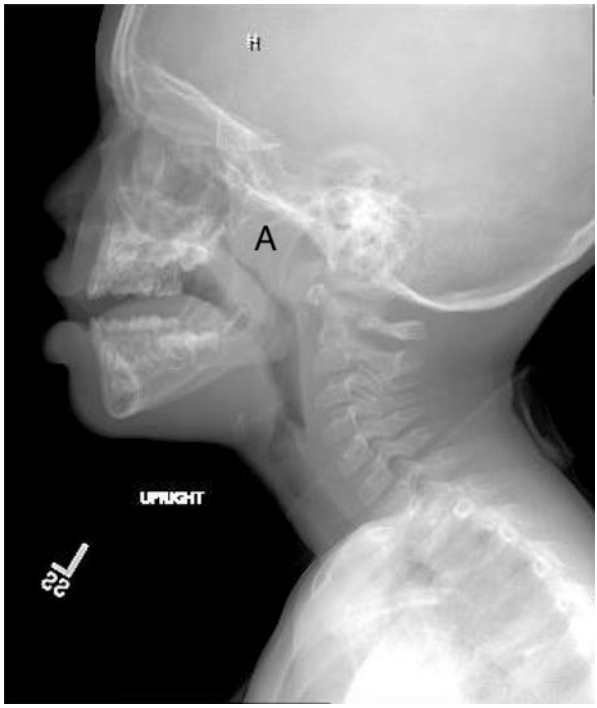


Fig. 20.4 Lateral neck plain film of the airway, demonstrating radiographic view of adenoid hypertrophy filling the nasopharynx and nearly abutting the soft palate. "A" denotes the adenoid

tool to determine need for otolaryngology referral. It may also serve as a useful tool in preoperative assessment for patients that may not tolerate awake endoscopic examination in the otolaryngology office.

There have been many proposed schema of linear and volume measurement [8], but the most commonly used method of radiographic measurement was described by Fujioka and colleagues in 1979 as the adenoid-to-nasopharyngeal (AN) ratio [37]. The adenoidal measurement (A) is defined as the distance from inferior margin of the adenoid at the point of maximal convexity to the anterior margin of the basi-occiput. The nasopharyngeal space (N) is measured from the posterosuperior edge of the hard palate to the anteroinferior sphenobasiocciput. The AN ratio is then obtained by dividing A by the value of N. Adenoid hypertrophy was defined as an AN ratio > 0.80. Brooks and colleagues [38] found that AN ratio correlated with the duration of apneas on polysomnogram, suggesting that lymphoid hyperplasia may affect the severity of obstructive sleep apnea.

Many studies have previously found a strong correlation of radiographic findings with degree of adenoid obstruction seen either on nasal endoscopy or intraoperative assessment [6, 7, 9, 39, 40]. Lertsburapa and colleagues [6] found that radiographic findings correlated well with adenoid visualization and that children who underwent radiographic assessment preoperatively tended to be younger than children who underwent awake endoscopic assessment. Caylakli and colleagues [7] found that AN ratio correlated well with nasal endoscopy findings, suggesting that lateral neck

radiographs may be an equally effective screening tool for adenoid hypertrophy. Saedi and colleagues [40] assessed endoscopic findings and lateral neck radiographic findings in 89 patients and found that symptoms of chronic mouth breathing and snoring were significantly correlated with adenoid size on lateral neck radiograph but not endoscopic findings. In a systematic review of lateral neck radiographs, Major and colleagues [8] reviewed 11 articles and reported that while lateral neck radiographs performed well in assessing overall adenoid size by radiologist interpretation and measurement, it was not as accurate in assessing overall nasopharyngeal size. In another systematic review of the utility of lateral neck radiographs, Feres and colleagues [41] also reviewed 11 articles, with some overlapping articles as the review by Major et al., and found that while most studies supported the use of lateral neck radiographs in assessing adenoid hypertrophy, many of the measurements are subjective, thus limiting the ability to widely recommend lateral neck radiographs as a standardized screening tool. Despite its limitations, lateral neck radiographs remain widely used and are helpful in assessing presence of adenoid hypertrophy, particularly in combination with the appropriate clinical history [42].

In addition to lateral neck radiographs, video fluoroscopy has been suggested as an additional radiographic assessment tool for adenoid size and hypertrophy. Ysunza and colleagues [43] compared the endoscopic findings with lateral neck radiographs and video fluoroscopy for 20 patients and found that video fluoroscopy showed 100% sensitivity and 90% specificity for diagnosis of adenoid hypertrophy, while lateral neck films showed 70% sensitivity and 55% specificity. Video fluoroscopy allows for dynamic evaluation of the nasopharynx and may provide information regarding the risk for velopharyngeal insufficiency, particularly in children who cannot tolerate awake endoscopic evaluation. However, videofluoroscopy is not as readily available as plan films and may not be as well understood by general practitioners as a screening tool. Computed tomography (CT) has also been suggested as an alternative radiographic tool for assessing adenoid hypertrophy; however CT poses a higher risk of radiation exposure and has not proven as a superior diagnostic tool [44, 45].

Radiographic imaging is rarely needed in the workup of allergic rhinitis. CT or magnetic resonance imaging (MRI) is generally only indicated when there is a suspicion for complications of rhinitis or when there are comorbidities such as rhinosinusitis and/or nasal polyposis [23].

Cephalometric analysis based on plain films of the skull/head has been suggested in the diagnosis of obstructive sleep apnea [46]. Kawashima and colleagues [47] found that patients with obstructive sleep apnea were more likely to have retrognathic findings on plain films and were also more likely to have a narrow pharyngeal airway. Ozdemir and colleagues [48] studied the cephalometric measures from plain film for 39 children and found that certain cephalometric measurements, including cranial skull base angles, positively correlated with AHI, while the minimal posterior airway space and length of mandibular plane were negatively correlated with AHI. However, given the diagnostic superiority of polysomnography and risk of radiation to children, radiographic assessment for obstructive sleep apnea is not commonly practiced.

Nasal Endoscopy

Flexible fiber-optic nasal endoscopy (Fig. 20.5) is a well-accepted instrument used routinely by otolaryngologists for visualization of the upper airway. Use of a flexible endoscope allows for evaluation of the nasal cavity and nasopharynx for septal deviation, turbinate hypertrophy, adenoid hypertrophy in addition to conducting a pharyngeal, and laryngeal examination. Flexible endoscopy also avoids radiation associated with lateral neck radiographs and has been advocated as the best method to assess adenoid hypertrophy in children [49, 50]. While nasal endoscopy may be difficult in some children, overall, it is a well-tolerated examination providing dynamic information and three-dimensional assessment of the nasopharynx and is thus regarded as a superior diagnostic tool compared to lateral neck radiographs. Aside from a small subset of patients who may be unable to tolerate endoscopy, flexible nasal endoscopy generally has few complications [50]. Occasionally, flexible nasal endoscopy cannot be performed due to severe turbinate hypertrophy, which has been reported in 2.3–4.1% of attempted flexible endoscopy [51, 52].

A prospective study by Wang and colleagues [10] on 180 children reported that findings on nasal endoscopy corresponded well with nasal obstruction symptoms and snoring, as well as tympanometry findings. The ability to visualize the adenoid and its relative degree of nasopharyngeal obstruction has been found to correlate well with intraoperative findings of adenoid hypertrophy and choanal obstruction [6]. In a cross-sectional study of 130 patients, Kindermann and colleagues [52] found a sensitivity of flexible nasal endoscopy for adenoid hypertrophy of 92% and a specificity of 71% with strong inter-rater reliability. Lertsburapa and colleagues [6] found that flexible nasal endoscopy findings correlate well with intraoperative

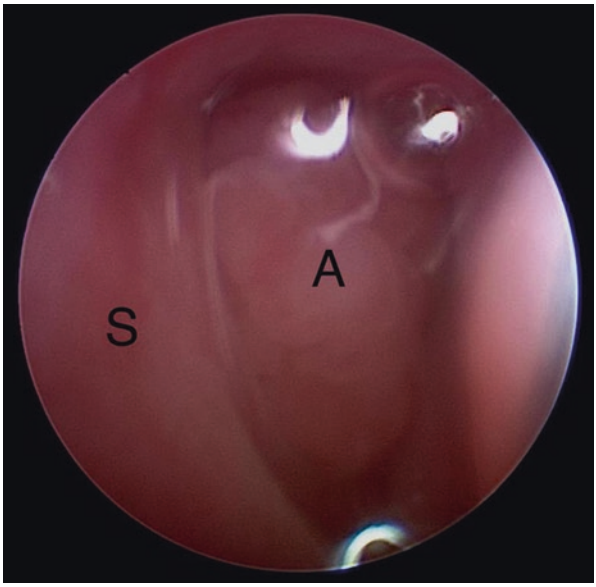


Fig. 20.5 Nasal endoscopy view of adenoid hypertrophy in the back of the nasal cavity, with the adenoid pad filling the choana. “S” denotes the nasal septum; “A” denotes the adenoid

assessment of adenoid hypertrophy. Cho and colleagues [53] also found a high correlation between AN ratio and endoscopic measurement of adenoid size.

Despite superior three-dimensional assessment of the nasopharynx and ability to visualize dynamic motion of the adenoids, flexible nasal endoscopy remains a relatively subjective practice. Various grading schema of adenoid size have been proposed. In 1992, Wormald and Prescott [54] suggested grading based on percentage of nasopharyngeal space obstruction. This has been often simplified into a four-category scheme: small <50%, medium 50–75%, and large >75% [52]. Havas and Lowinger [55] proposed another four-category grading system based on percentage of obstruction during intraoperative endoscopic assessment: grade 0 = 0–30% obstruction, grade 1 = 30–59% obstruction, grade 2 = 60–99% obstruction, and grade 3 = 100% obstruction. Cassano and colleagues [56] described in 2003 another classification schema as follows: 1st degree with no obstruction and/or scarce presence of adenoid tissue in the nasopharynx, 2nd degree with adenoid obstruction confined to the upper half of the nasopharynx resulting in sufficiently patent choana and clear tube ostia, 3rd degree with up to 75% involvement of the nasopharynx with considerable obstruction of the choana and partial tube ostia obstruction, and 4th degree with completion obstruction of the nasopharynx by adenoid tissue. Under this classification system, recommendations for adenoidectomy were made in for patients with a 4th degree obstruction, while recommendations against surgical intervention were given to patients with 1st and 2nd degree obstruction as these patients were more likely to have nasal obstruction due to allergic rhinitis or craniofacial pathologies. For patients with a 3rd degree of obstruction, other etiologies such as allergic rhinitis or sinusitis should also be considered. In 2006, Parikh and colleagues [49] proposed a validated, four-category classification system based on the anatomic relationship of the adenoid to surrounding structures, specifically grade 1, no contact with other anatomic structures: grade 2, contact with the torus tubarius; grade 3, contact with the torus tubarius and vomer; and grade 4, contact with the torus tubarius, vomer, and soft palate. While practitioners may favor one classification system over another, there is still a lack of a single standardized grading system.

Generally, nasal endoscopy is not needed in the diagnosis of allergic rhinitis. The use of nasal endoscopy in the diagnosis of allergic rhinitis is limited to refractory cases, when symptoms/physical examination are atypical or when complications are suspected [23]. In a study of 54 children, Kubba and Bingham [51] found that 63% of patients with nasal obstructive symptoms had adenoid hypertrophy; 75% of patients had other identifiable sources of obstruction (rhinitis, septal deviation). Furthermore, 29% of patients were found to have turbinate hypertrophy consistent with allergic rhinitis. Nasal endoscopy allows for superior visualization of the upper airway anatomy, allowing for more accurate identification of the etiology of nasal obstruction.

Acoustic Rhinometry

Acoustic rhinometry provides an assessment of the cross-sectional area of the nasal cavity and nasopharynx as a function of distance using acoustic methods and has

also been applied toward investigating the geometry of the pharyngeal, laryngeal, and tracheal airway [57]. The basis of acoustic rhinometry is the measurement of reflected sound waves which is distorted by local acoustic impedances secondary to anatomic surfaces within the nasal cavity. The cross-sectional area is estimated from the magnitude of sound wave distortion, and changes in the reflected sound wave are used to estimate the distance of the reflective anatomy. Acoustic rhinometry has been validated in comparison to radiographic measurements of nasal cavity cross-sectional area. A trigger module produces an acoustic pulse, which conducts to the nasal cavity via a wave tube and nose piece, and reflected sound waves are recorded by a microphone. After digitization of the data, it is then converted into an area-distance function.

Cho and colleagues [53] found that acoustic rhinometry was useful in calculating an adenoid to nasopharynx ratio, which correlated well with endoscopic findings. Additionally, they reported that acoustic rhinometry could also be used to compare nasopharyngeal cross-sectional area pre- and postoperatively. As such, they concluded that acoustic rhinometry may serve as useful of a screening tool as nasal endoscopy. Mostafa [58] reported a 93.5% positive predictive value of acoustic rhinomanometry compared to lateral neck radiographs in adenoid assessment among children presenting with symptoms suggestive of adenoid hypertrophy. On the contrary, Riechelmann and colleagues [59] found no statistical difference on acoustic rhinometry results comparing symptomatic preschool children (with snoring, nasal obstruction, and/or mouth breathing) with age-matched controls. In this study, acoustic rhinometry was also unable to measure significant differences pre- and postadenoidectomy.

Acoustic rhinometry has been used to assess nasal cavity patency and size in the assessment of allergic rhinitis pre- and posttreatment. Chawes and colleagues [60] utilized acoustic rhinometry in the measure of allergic versus nonallergic rhinitis in 255 children surrounding pollen season; they reported that patients with a diagnosis of allergic rhinitis were associated with reduced nasal airway patency on acoustic rhinometry that was irreversible with pretesting topical decongestant. The utility of acoustic rhinometry in the management of allergic rhinitis may be to monitor response and adherence to medical therapy. Nielsen and colleagues [61] used acoustic rhinometry to assess the effect of nasal corticosteroids on nasal cavity patency before and after peak pollen season. Nasal provocation testing, in which nasal mucosa is exposed to airborne allergens, can be performed in conjunction with acoustic rhinometry for objective measurements of the nasal cavity response to specific allergens [62].

Acoustic rhinometry may have utility to diagnosing the size and location of upper airway obstruction [63]. Morris and colleagues suggest that acoustic rhinometry may help diagnose nasal obstruction in patients with persistent OSA [64]. In a study of 203 children, Monahan and colleagues [65] reported that acoustic pharyngometry findings were useful in evaluation of sleep-disordered breathing. In particular, this study found that the minimal cross-sectional area of was predictive of sleep disordered breathing.

In theory, acoustic rhinometry may be a reliable, reproducible, noninvasive method capable of obtaining valuable information on the cross-sectional area of the

nasal cavity and nasopharynx and is well tolerated by children [66]. However, acoustic rhinometry in assessing adenoid hypertrophy is not currently widely accepted practice. Normative, age-specific data on minimal cross-sectional areas have yet to be established [66]. When using acoustic rhinometry to assess for adenoid hypertrophy, some practitioners advocate for the use of nasal decongestants to aid in eliminating the possible effects of nasal cavity mucosal edema from chronic rhinitis [53, 67]. Caution should be given toward the use of topical decongestants, as they may affect measurements of the posterior nasal airway, and there is a lack of consensus surrounding decongestive procedures [68]. Findings on acoustic rhinometry do not necessarily correlate with patient perception of airflow and may be inaccurate in the setting of copious nasal secretions [23]. While acoustic rhinometry may be well tolerated in the pediatric population, performance requires specialized equipment and software that may not be readily available in an otolaryngology office. As such, it is not currently a commonly used method of assessing for nasal obstruction or adenoid hypertrophy [69].

Rhinomanometry

Unlike acoustic rhinometry, which is a test of nasal geometry, rhinomanometry is a test of nasal function and serves as complementary to the former. Rhinomanometry allows for objective evaluation of nasal airway patency. During testing, the patient is given a face mask measuring nasal airflow, and pressure tubing is placed transorally into the oropharynx, postnasal through the nasal cavity or anterior to the nostril. Passive airflow is tested by measuring the pressure of air passing through the patient's nose while the patient holds his/her breath. Active airflow uses the patient's own inhalation and expiration as the source of air pressure and flow. Active anterior rhinomanometry is most often used as it measures quiet respiration and is easily performed. Nostrils can be measured one at a time or jointly. The measurement of airflow and transnasal pressure during respiration allows for calculation of nasal airflow, and nasal airway resistance at a defined transnasal pressure is performed [70, 71]. The resulting rhinomanogram is S-shaped curve displaying the relationship between nasal airflow and transnasal pressure during the breathing cycle. Provocation testing may also be performed when assessing for allergic rhinitis. It should be noted, however, that as nasal airflow is non-laminar, and transitional (a mixture of laminar and turbulent flow), it does complicate calculations of transnasal resistance and may vary among devices [72].

In a cross-sectional study of anterior active rhinomanometry in 192 healthy Caucasian children, Zapletal and Chalupova [70] found that with increases in age and growth correlated with increases with nasal airflow and reductions in nasal airway resistance. It has been found that rhinomanometry scores following nasal decongestion were highly correlated with nasal endoscopic findings for children with a low degree of adenoid obstruction and those with a high level of obstruction [73, 74]. Following application of a nasal decongestant to address potential anterior nasal mucosal edema, rhinomanometry may be helpful in diagnosing and monitoring the

severity of nasal obstruction due to adenoid hypertrophy. Parker and colleagues [72] reported that among 1000 consecutive children referred for active posterior rhinomanometry, only 1.4% of patients were unable to complete the examination, of which the majority was less than 5 years of age. However, another study assessing the utility of anterior active rhinomanometry in patient selection for adenoidectomy compared to adenoid depth as seen on lateral neck radiographs found that rhinomanometry was difficult and time-consuming to perform in children and did not significantly correlate with radiographic findings [75]. van Cauwenberge and colleagues [76] reported that rhinomanometry in children yielded results with large standard deviations and that changes in body position led to variations in measurements of nasal resistance.

Rizzi and colleagues [77] performed anterior rhinomanometry in 73 patients who presented with adenotonsillar hypertrophy and sleep-disordered breathing. This study concluded that anterior rhinomanometry as an assessment of airway patency was reliable and that children with adenotonsillar hypertrophy and increased nasal resistance likely to have OSA; they reported that having a nasal resistance value of 0.59 Pa/cm^3/s was 91% sensitive and 96% specific for identifying the children with adenotonsillar hypertrophy. However, the use of anterior rhinomanometry in the diagnosis of OSA is not yet validated [28].

Rhinomanometry may be used to estimate nasal obstruction in the setting of allergic rhinitis. Like acoustic rhinometry, rhinomanometry may be used to obtain objective measurements on the response to pharmacologic therapy [23]. Rhinomanometry can also be used for objective measurements following nasal provocation testing for airborne allergens [62]. However, rhinomanometry findings may not directly correlate with subjective reports of nasal obstruction. Furthermore, while rhinomanometry is able to assess for potential areas of nasal airway obstruction, it is not considered a substitute for nasal endoscopy and visualization of anatomic abnormalities. Given the ease of obtaining lateral neck radiographs and performing flexible endoscopic examinations in the office, rhinomanometry is not commonly used today in clinical practice [76].

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Allergic Rhinitis and Sleep: Approaches to Management

21

Camil Correia and Fuad M. Baroody

Allergic rhinitis is an IgE-mediated immune reaction of the nasal mucosa to foreign substances (allergens) characterized by sneezing, nasal congestion, rhinorrhea, and nasal itching often accompanied by red, watery, itchy eyes, thus the term rhinoconjunctivitis. For these symptoms to occur, various key pathophysiologic responses must be present and will be described briefly. Initially, the nasal mucosa is exposed to an allergen of which there are many varieties. The allergen is processed by antigen-presenting cells (such as macrophages, dendritic cells, and Langerhans cells), and portions of it are then presented to helper T cells as well as class II MHC molecules [1, 2]. Helper T cells then secrete cytokines promoting growth and differentiation of other immune cells involved in the allergic response. The helper T cells are of the TH2 CD4+ variety and are responsible for secretion of cytokines such as IL-4, IL-5, and IL-13 [3]. IL-4 and IL-13 are key molecules involved in the upregulation of production of allergen-specific IgE by plasma cells, and IL-5 is important in the recruitment and survival of eosinophils, key cells in the allergic response [3–5]. Allergen-specific IgE attaches to high-affinity receptors on mast calls and basophils as well as low-affinity receptors on other cell types creating a sensitized nasal mucosa [6].

On subsequent exposure to the allergen, these specific IgE antibodies serve as receptors for the antigen. Cross-linkage of IgE on mast cells leads to the release of stored and newly synthesized inflammatory mediators such as histamine, tryptase, prostaglandins, leukotrienes, and platelet-activating factor [3, 7]. These stimulate

C. Correia (✉)
Department of Surgery, Section of Otolaryngology-Head and Neck Surgery, The University of Chicago Medicine, Chicago, IL, USA
e-mail: Camil.Correia@uchospitals.edu

F. M. Baroody
Department of Surgery, Section of Otolaryngology-Head and Neck Surgery and Department of Pediatrics, The University of Chicago Medicine and The Comer Children's Hospital, Chicago, IL, USA

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nerves, glands, and blood vessels to cause the hallmark symptoms of allergic rhinitis: sneezing, itching, rhinorrhea, and nasal congestion. This is referred to as the acute-phase response. A subset of patients experience recurrence of symptoms mostly characterized by nasal congestion with a peak 6 hours following exposure and resolution within 24 hours, known as the late-phase response [7, 8]. This is accompanied by the release of histamine, and mediators of vascular permeability (albumin) as well as eosinophil markers (major basic protein and eosinophil cationic protein). There is also an influx of inflammatory cells and cytokines including eosinophils and IL-5, IL-6, and IL-8 [5]. Studies using immunohistochemistry to stain nasal mucosal biopsy specimens show higher numbers of IL-4-positive cells in patients with allergic rhinitis compared to non-allergic controls [9]. IL-4 co-localized to mast cells in these biopsy specimens suggesting that, in addition to TH2 cells, mast cells are also responsible for the production of pro-inflammatory cytokines [9, 10]. IL-5 and IL-6 were also shown to co-localize to mast cells in allergic subjects. Pretreatment with intranasal steroids suppressed IL-4 expression within mast cells in the nasal submucosa of patients with seasonal allergic rhinitis [11]. Other studies using in situ hybridization to evaluate mRNA for the various cytokines have demonstrated significantly high expression of the TH2 cytokines, IL-4, IL-5, and IL-13 in nasal mucosal biopsies obtained from allergic patients following allergen exposure [12, 13]. Likewise, levels of activated eosinophils were increased post-exposure detected via mRNA expression of EG2 + [14]. All of these molecular studies indicate that both T lymphocytes and mast cells play crucial roles in the production of cytokines and maintenance of the inflammatory state post-allergen exposure, which is characterized by eosinophilic infiltration of the tissue.

The cellular changes induced by this increase in cytokines include increased numbers of eosinophils in the nasal secretions and the mucosa within 1–2 hours of exposure to a challenge and during natural allergic disease. Increases in basophils are also noted and are thought to be responsible for late increases in histamine [14–16]. When biopsy specimens are examined, eosinophils are not the predominant cell type recovered, rather lymphocytes and mast cells predominate. Eosinophils, however, tend to be more numerous in nasal secretions when these are sampled.

This background of inflammation in the allergic nasal mucosa and secretions is thought to be key in the observed phenomenon of hyperresponsiveness of allergic individuals to both specific and nonspecific stimuli. Priming, the term given to hyperresponsiveness to the allergic stimuli themselves following repeated exposure, is a key feature of allergic rhinitis [7, 17, 18]. Patients experience progressively worse symptoms throughout the allergy season secondary to this phenomenon. In nasal challenge studies conducted to elucidate this phenomenon, subjects were challenged with relevant allergen in the laboratory on consecutive days and their nasal response monitored. Twenty-four hours after initial exposure, patients with allergic rhinitis were noted to have an increase in severity of sneezing upon repeated challenge as well as a lower dose of allergen to generate a comparable response to the first-day responses. These changes were mirrored by higher numbers of neutrophils, eosinophils, and basophils. This lowered responsiveness threshold for antigen

after repeated exposure is also present in response to nonspecific irritants [19]. During the allergy season, this is seen when allergic patients are more symptomatic in response to cigarette smoke, pollution, or strong perfumes than they would usually be outside of their allergic season. In the laboratory, this has been demonstrated by increased reactivity to histamine and methacholine after a preceding allergen challenge [19, 20].

In summary, allergic rhinitis is a clinical disease marked by initial sensitization to allergen, initial and delayed responses within the nasal mucosa, and persistent inflammation leading to both specific and nonspecific hyperresponsiveness. Although not discussed in this chapter, there are also various neuronal reflexes mediating changes seen distant to the sites of antigen exposure in the eye, sinuses, and lower airways in response to nasal allergen exposure.

The prevalence of allergic rhinitis in the United States has been reported between 4 and 40% of the population, and the incidence is rising [21, 22]. Typically, patients require years of low-level exposure prior to development of symptoms, and thus the disease is rarely seen in children younger than 2 years [23]. In contrast, following the age of 2, children and adolescents are more likely to be affected than adults, with typical initial presentation prior to the age of 20. Patients experience relatively stable symptoms through early adulthood and then in middle age are noted to have improvement. In childhood, boys are more likely to be affected.

The incidence of allergic rhinitis has been rising since the 1970s along with other allergic diseases (asthma and atopic dermatitis) [23–26]. There have been multiple theories regarding the significance of the increased rates of atopy in the population, but the leading theory surrounding this development is the hygiene hypothesis [27]. These increases in atopy are primarily found in developed countries with coincident decreases in infectious diseases associated with antibiotics, vaccines, and improved hygiene. There are interesting studies linking both birth order and geography to likelihood of development of some form of atopy [27–29]. Children with older siblings or attendance in daycare are less likely to develop asthma, and the administration of antibiotics under the age of one has been associated with an increased risk of development of asthma and atopic conditions [30–32]. Geographically, there is a lower incidence of atopy approaching warmer latitudes in both the Northern and Southern Hemisphere, with some attributing this to differences in socioeconomic status, while others theorize that differences in ambient temperature and bacterial burden account for these differences [33–35]. Another theory rests on the explanation that decreases in vitamin D are crucial to the development of atopic conditions due to chronic inflammation and its ability to promote IL-10 production by T regulatory cells [36–40]. Similarly, suburban versus urban dwelling has significant impact on the development of allergic rhinitis and asthma. Farm dwelling in early childhood is protective against the development of allergic rhinitis across multiple studies, and this is thought to be related to an imbalance between TH1 and TH2 responses [34, 41, 42].

The genetic basis for these diseases should not be neglected. Children of parents with allergic conditions are more likely to experience atopy, the production of

IgE-specific antibodies. If neither parent has allergies or asthma, their offspring had a 13% incidence of atopy, while those children with one parent affected have a 29% incidence and 47% of children with both parents affected are likely to have atopy themselves [23, 43]. Similarly, patients with a history of asthma are four to six times more likely to develop allergic rhinitis [44].

Clinical Picture

Allergic rhinitis is characterized by recurrent episodes of sneezing, pruritus, rhinorrhea, nasal congestion, and watery/itchy eyes, thus the term rhinoconjunctivitis. Allergic rhinitis can be classified as seasonal, perennial, or episodic depending on the chronicity of symptoms. Typically, seasonal allergens include grasses and trees, which affect patients during the spring months, and ragweed, which predominates in the fall. This pattern is different in different parts of the United States and the world. Perennial allergens are usually indoor and include dust mites, indoor molds, and household pets. Episodic allergic rhinitis is a term given to patients with reactivity to allergens that they are exposed to sporadically such as a cat allergy only elicited when infrequently visiting a household with cats. According to the World Health Organization's Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, allergic rhinitis can also be classified as intermittent or persistent [45]. Intermittent AR describes symptoms occurring less than 4 days per week or for less than 4 weeks in the year, while persistent AR is symptoms present more than 4 days per week or for more than 4 weeks in the year. Severity is also addressed in the ARIA classification based on interference of the symptoms with quality of life of the patients. The disease is mild if there is no negative impact on quality of life measures (sleep, daily activities, sports, leisure, work/school) and moderate to severe if there is.

Allergic rhinitis results in significant impairment in both disease specific and general measures of quality of life including lost productivity, diminished cognitive function, and effects on emotional well-being [21]. When assessing the economic burden of allergic rhinitis in adults, investigators take into account both the increased direct costs to patients and insurance providers, and the indirect costs of absenteeism and decreased productivity [21]. It is estimated that adults spend between US $2 and $5 billion yearly treating symptoms of allergic rhinitis. In addition to monies spent, the US economy has a high indirect cost from allergic rhinitis, estimated between $2 and $4 billion yearly in lost productivity [46]. In children, up to 2 million school days are lost yearly due to allergic rhinitis and its comorbidities [47].

Effect of Allergic Rhinitis on Sleep

Patients with allergic rhinitis have increased difficulty falling asleep, more frequent nighttime awakenings, as well as subjective sense of inadequate quality of sleep [48]. Close to 70% of patients with perennial allergic rhinitis and approximately 50% of seasonal allergic rhinitis patients report interference with sleep [22]. The major impact on sleep is thought to be mediated by nasal congestion, which is often the predominant symptom in allergic rhinitis, leading to mouth breathing [49]. The obstruction related to nasal inflammation and increased nasal resistance can increase respiratory and arousal events as well as lead to increased sleep fragmentation [50]. These effects are noted in both adult and pediatric populations. Recent survey data show that anywhere between 25% and 40% of parents of school-aged children perceive a negative impact of their children's allergies on sleep [51]. Moreover, when comparing children with allergic rhinitis to those without allergies, there are significant increases in difficulty falling asleep (32% vs 12%) and nighttime awakening (26% vs 8%) [51]. In addition to nasal congestion, adenotonsillar hypertrophy plays an important role in childhood sleep-disordered breathing, and there is some evidence that allergic rhinitis might be a contributor. In a comparison of two groups of children, with and without adenotonsillar hypertrophy, Sadeghi and colleagues reported that 70% of the children with adenotonsillar hypertrophy had positive skin tests to common allergens compared to an incidence of only 10% of the control group who did not have adenotonsillar hypertrophy [52]. In another study, 39 children with snoring presenting for polysomnography underwent RAST testing. Subjects with positive RAST had a significantly higher frequency of confirmed sleep apnea (57%) compared with the RAST-negative group (40%) [53]. With the caveat that a positive serum or skin prick allergy test alone is not necessarily a predictor of positive clinical allergic disease, these studies do suggest a relationship between allergies and adenotonsillar hypertrophy and sleep-disordered breathing.

Given the high impact of allergic rhinitis on health and health-related quality of life as well as its increasing incidence, treatment options available should be easily administered, cost-effective, and safe. To date, several treatment options have been tested and approved, while others continue to be evaluated for safety and efficacy. In addressing patients with concomitant sleep-disordered breathing, it is important to address nasal congestion and obstruction as these are the most common symptoms impacting sleep. Multiple studies have indicated that various forms of treatment of allergic rhinitis also have a positive impact on sleep-related symptoms.

Approaches to the Management of Allergic Rhinitis

Avoidance

Avoidance of offending allergens is considered the first line of treatment for allergic rhinitis. These measures are typically targeted at controlling indoor allergens,

especially dust mites, animal danders, and molds. Exposure to outdoor allergens, such as grass, tree and weed pollens, and outdoor mold spores, is very difficult to control.

A recent systematic review demonstrated that single measures targeted at house dust mite are not effective in reducing symptoms in patients with allergic rhinitis [54]. In another review of placebo-controlled trials, the authors conclude that the use of acaricides and extensive bedroom-based environmental control programs are beneficial in reducing rhinitis symptoms due to dust mites [54]. Of importance, the isolated use of dust mite-impermeable bedding is unlikely to prove effective. Supporting these conclusions, a large study investigated the effects of allergen-impermeable casings in patients with mite-induced rhinitis and showed that mattress and pillow covers reduced the levels of mattress dust mite allergen Der p 1 by 30% of baseline but resulted in no difference in the clinical symptoms of allergic rhinitis [55].

A number of different strategies have also been used to reduce cat allergen in homes. One study has demonstrated that several preventive measures including removal of carpeting, tannic acid application, washing bedding, and washing the cat resulted in a reduction of levels of Fel d 1 in the house and abatement of clinical symptoms of allergic rhinitis [56]. HEPA (high-efficiency particulate air) filters also have been used as a solitary means to reduce symptoms and have not been found effective [57]. Washing cats by immersion lowers levels of airborne Fel d1, but the decrease is not maintained after 1 week [58]. Overall, the most effective approach to reduction of indoor cat allergen is removal of the cat from the indoor environment. Even this measure, however, may not be immediately effective, because residual allergen may remain at relatively high levels in the carpeting and upholstered furniture for several months or longer [57]. After removal of the cat, therefore, all carpeting should be taken up and upholstered furniture cleaned. As for hypoallergenic breeds, so-called hypoallergenic dogs had higher Can f 1 levels in hair and coat samples than did control breeds and airborne levels of allergen was not different between breeds [59].

In general, although some avoidance measures are effective in lowering the level of allergens in the house, they do not always lead to an improvement in symptoms. Therefore, most patients have to resort to pharmacotherapy in addition to the above measures. Data regarding the effect of avoidance of allergens on sleep in allergic rhinitis is limited.

Saline Irrigation

The utility of nasal saline irrigation to lower the burden of infected secretions and improve mucociliary clearance in chronic rhinosinusitis has long been recognized. Recent studies in Italy demonstrated that for children with perennial allergies, nasal saline irrigations were both well tolerated as well as effective in reduction of rhinitis scores as well as the need for antihistamine medications [60, 61]. In a systematic review and meta-analysis, isotonic saline irrigations were also found to result in decreased nasal symptoms, decreased use of pharmacotherapy, and improvement in quality of life in patients with allergic rhinitis [62]. Measures of improvement in

quality of life utilized in these studies included the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), which measures allergic rhinitis' impact on six physical and emotional domains, one of which is sleep. However, the outcomes of saline use as relates to the individual domains are not reported [62]. These results support the use of saline irrigation in the management of allergic rhinitis, and more data is required to assess its impact on sleep-related symptoms.

Systemic Antihistamines

Antihistamine pharmacotherapy has been a mainstay of allergic rhinitis treatment for years. H1 antihistamines work as inverse agonists by combining with and stabilizing H1-receptors in the inactive conformation. Drugs within this class include both the first-generation and second-generation antihistamines. First-generation drugs, such as diphenhydramine, are lipophilic and have anticholinergic and sedating side effects, while second-generation drugs, such as loratadine, fexofenadine, and cetirizine, are less lipophilic and have minimal side effects due to their inability to cross the blood-brain barrier. In addition, second-generation antihistamines have a longer half-life allowing for once-daily administration [63]. The drugs within this class are effective in controlling histamine-mediated symptoms such as sneezing, itching, rhinorrhea, and ocular symptoms including itchy and watery eyes. They are not as effective in controlling nasal congestion, which is usually the most bothersome symptom for patients [63, 64]. Advantageously, antihistamines are rapidly absorbed with onset of action within 1 hour of administration. Furthermore, as AR is most commonly diagnosed in the pediatric population, this class of drugs has been shown to be both safe and effective in children even when administered long term [65].

The most limiting factor in the use of antihistamines is their side effect profile. First-generation drugs (diphenhydramine, hydroxyzine, chlorpheniramine, brompheniramine, and clemastine) are sedating for 20% of patients [63]. Additionally, they can lead to drying of secretions secondary to their anticholinergic properties. A study examining learning scores in children found that at baseline children with allergic rhinitis had poorer scores than those without AR but these children did significantly worse than those receiving placebo following administration of first-generation antihistamines for 2 weeks. Another group receiving a second-generation antihistamine, loratadine, performed better than those on placebo and was not significantly different from their non-allergic peers [66]. Thus, first-generation antihistamines should be avoided in children due to their effects on the central nervous system. Second-generation antihistamines are often available in liquid form, and some have approvals by the US Food and Drug Administration (FDA) for use in children as young as 6 months of age. Although the FDA labels for cetirizine and levocetirizine indicate they are sedating, this is significantly less than first-generation antihistamines. First-generation antihistamine preparations should be avoided in those experiencing daytime somnolence and fatigue due to allergic rhinitis as these medications have minimal effects in reducing nasal congestion and may increase sedation. Some studies indicate improvement in sleep and quality of life with use of

second-generation oral antihistamines, which should be the preferred recommended therapy for allergic rhinitis when this class is considered [67].

Intranasal Antihistamines

Antihistamines are also available for intranasal administration as azelastine or olopatadine hydrochloride (0.6%) with an onset of action within minutes. Azelastine is comparable in efficacy to other drugs in this class against symptoms of itching, sneezing, and runny nose and additionally has positive effects on nasal congestion [68]. In fact, patient's failing oral antihistamines may respond to intranasal preparations [69]. These are typically administered twice daily and can have side effects of somnolence and alterations in taste immediately following use. Both preparations have been studied in children and are approved for use in children 6 years and older [68]. Data regarding intranasal antihistamines and effects on sleep are mixed with some studies demonstrating improvement in quality of sleep and proportion of mouth breathing, while others indicate increased daytime somnolence as a side effect of these agents [70, 71].

Decongestants

Decongestants include topical as well as systemic agents that cause vascular constriction and reduction in nasal blood supply by alpha-adrenergic stimulation. Topical decongestants include catecholamines (phenylephrine) or imidazoline derivatives (xylometazoline or oxymetazoline). These agents have a rapid onset of action and are highly efficacious without systemic side effects, except in children where there have been reports of seizures. The major concern with these agents is the development of rhinitis medicamentosa or rebound nasal congestion when these agents are used for a length of time and then discontinued. Systemic decongestants include pseudoephedrine hydrochloride and phenylephrine. They are not associated with rhinitis medicamentosa but are less efficacious at relieving nasal congestion and have less favorable side effect profiles than their topical counterparts. Pseudoephedrine availability has been restricted to behind the counter in the United States since 2006 because it could be used in the manufacture of methamphetamine. Oral decongestants have systemic effects with up to 25% of patients experiencing insomnia and irritability. Hypertension, nervousness, renal failure, arrhythmias, psychosis, strokes, and seizures can be caused by overdose. As such oral decongestants are not recommended for patients with hypertension, heart disease, seizure disorders, hyperthyroidism, or those on monoamine oxidase inhibitor therapy. In addition to an unfavorable side effect profile, phenylephrine has been shown in meta-analysis to lack efficacy for nasal congestion when compared to placebo using both objective and subjective measures [72]. There is no evidence to support the use of oral decongestants as monotherapy for managing sleep-related symptoms of allergic rhinitis.

Anticholinergics

Another category of medications for therapy of allergic rhinitis is anticholinergics. These medications are most appropriate for patients with sole complaints of clear rhinorrhea. In this category, ipratropium bromide is administered intranasally to relieve rhinorrhea, but it has no effect on sneezing or congestion [20]. There is little or no systemic absorption, and it can be used in conjunction with other modalities. Studies utilizing ipratropium bromide in patients with allergic rhinitis indicate some improvement in quality of life indicators, but, not surprisingly, sleep was not among them as these agents do not have a significant impact on nasal congestion [73].

Cromolyn Sodium

This is a readily available over the counter as a 4% intranasal solution, which is effective for symptoms of sneezing, itching, and rhinorrhea. The mode of action is not known, but its excellent safety profile makes it an option for use in pregnant women and children; however, efficacy is limited by the potential for poor compliance due to its four to six times per day dosing [74]. Studies examining the effects of cromolyn sodium on sleep in allergic rhinitis have not been performed to date.

Leukotriene Modifiers

The most commonly used agent in this category is montelukast, a leukotriene receptor antagonist. It is the only leukotriene modifier approved by the FDA for use in allergic rhinitis. It has been shown in multiple clinical trials to be more effective than placebo as well as equal in efficacy to antihistamines in controlling the ocular and nasal symptoms of allergic rhinitis [75, 76]. In addition, montelukast demonstrated significant improvement in daytime somnolence and daytime fatigue over placebo in a small double-blind crossover trial [77]. Montelukast has been approved for use in adults and children for both seasonal (greater than 2 years of age) and perennial allergic rhinitis (greater than 6 months of age). Because efficacy is limited and comparable to that of antihistamines, leukotriene receptor antagonists are not recommended for first-line monotherapy in allergic rhinitis [46]. Since these agents are also beneficial for the treatment of asthma, patients with both asthma and allergic rhinitis might be ideal candidates for this therapy. In addition, montelukast is an alternative therapy for the treatment of mild obstructive sleep apnea in children with a randomized controlled trial demonstrating improvement in apnea-hypopnea index as measured by polysomnography [78]. The side effects are typically minimal; however, they can rarely include neuropsychiatric events such as aggression, depression, suicidal thinking, and behavior [79].

Intranasal Corticosteroids (ICSs)

ICSs are some of the most studied and most efficacious therapies for allergic rhinitis available. They are effective because of their anti-inflammatory properties, which both decrease the presence of mediators and cytokine release and inhibit the recruitment of inflammatory cells such as basophils, eosinophils, neutrophils, and mononuclear cells into the nose. Multiple placebo-controlled clinical trials demonstrate that intranasal steroids are effective against the most common symptoms of allergic rhinitis including sneezing, itching, rhinorrhea, and congestion in both adults and children [80, 81]. Further studies indicate that the hyperresponsiveness of the nasal mucosa is also diminished by use of intranasal corticosteroids. Additionally, ocular symptoms, such as itching, tearing, redness, and puffiness, are reduced [82, 83]. This is likely due to inhibition of the naso-ocular reflex which is at least partially responsible for the eye symptoms in allergic rhinoconjunctivitis [84]. These reductions in symptoms lead to improvement in quality of life and sleep. Multiple intranasal corticosteroids have been found to reduce sleep-related symptoms including daytime fatigue and somnolence [85]. In children with OSA, a randomized controlled trial demonstrated that a 6-week trial of fluticasone propionate led to decreased frequency of mixed and obstructive apneas on polysomnography [86]. In fact, the American Academy of Pediatrics clinical practice guidelines lists intranasal corticosteroids as an option for treatment of pediatric obstructive sleep [87]. Onset of action has been reported between 3 hours and 60 hours after initiation, and continuous use is recommended for maximal therapeutic benefit however as needed use of fluticasone has been shown to be superior to placebo [88, 89].

In comparison to other medications for allergic rhinitis, intranasal steroids are superior to oral first-generation antihistamines in controlling nasal symptoms [80]. They are also more effective than leukotriene receptor antagonists [90]. There are several preparations of INCS, which have similar efficacy, and some are now available over the counter. Side effect profiles tend to be similar between preparations with differences noted by patients in aftertaste, smell, and throat rundown. The most common side effects include dryness, burning, blood-tinged secretions, and epistaxis secondary to local irritation. Concerning the potential risks of systemic absorption of steroids, there are no adverse effects on the hypothalamic-pituitary-adrenal axis as determined by monitoring of morning cortisol, cosyntropin stimulation and 24-hour urinary-free cortisol excretion [91]. Investigations have been conducted into the effects of INCS on growth in children looking at short-term and long-term growth. Regarding short-term growth, measured by knemometry, intranasal budesonide has been shown to reduce growth rate; however, this effect was not seen in placebo-controlled trials examining fluticasone furoate, triamcinolone acetonide, and fluticasone propionate. Long-term growth as measured by stadiometry over a year, in participants receiving beclomethasone dipropionate at double the recommended daily dosage, resulted in growth suppression [92]. Fluticasone propionate and mometasone did not have similar effects [91, 93]. All intranasal corticosteroids are FDA approved for use in children, and guidelines for dosages within age ranges are provided in Table 21.1.

Table 21.1 Common intranasal steroid/combination preparations

Chemical name	Trade name	Formulation	Dose/Actuation	Recommended dosage
Triamcinolone	Nasacort®[a]	Propellant, aqueous	55 mcg	*2–5 years:* 1 spray/nostril QD (110mcg daily) *6–11 years:* 2 sprays/nostril QD (220 mcg daily) *≥12 years:* 2 sprays/nostril QD-BID (220 mcg–440 mcg daily)
Budesonide	Rhinocort Aqua® Rhinocort Allergy®[a]	Propellant	32 mcg	*6–11 years:* 1 spray/nostril QD or 2 sprays/nostril in AM (128 mcg daily) *>12 years:* 2 sprays/nostril QD or 4 sprays/nostril QD (256 mcg/daily)
Flunisolide	Nasalide® Apo-Flunisolide® Rhinalar®	0.025% solution	25 mcg	*6–14 years:* 1 spray/nostril TID (150 mcg daily) or 2 sprays/nostril BID (200 mcg daily) *≥14 years:* 2 sprays/nostril BID-TID (200–300 mcg daily)
Fluticasone propionate	Flonase Allergy Relief®[a]	0.05% nasal spray (aqueous)	50 mcg	*4 years–adolesc:* 1 spray/nostril QD (100 mcg daily)
				Adults: 2 sprays/nostril QD (200 mcg daily)
Mometasone furoate	Nasonex®	Aqueous	50 mcg	*2–11 years:* 1 spray/nostril daily (100mcg daily) *≥12 years:* 2 sprays/nostril once daily (200 mcg daily)
Ciclesonide	Omnaris®	Suspension	50mcg	*≥6 years:* 2 sprays/nostril QD (200 mcg daily)
Fluticasone furoate	Flonase Sensimist®[a]	Suspension	27.5mcg	*2–11 years:*1 spray/nostril QD (55 mcg daily) *>11 years:* 2 sprays/nostril QD (110 mcg daily)
Beclomethasone dipropionate	Qnasl®	Dry nasal aerosol	80 mcg	*4–11 years: 1 spray/nostril QD (80 mcg/daily)* *≥12 years:* 2 sprays/nostril QD (320 mcg daily)

(continued)

Table 21.1 (continued)

Chemical name	Trade name	Formulation	Dose/Actuation	Recommended dosage
Ciclesonide	Zetonna®	Dry nasal aerosol	37 mcg	*≥12 years:* 1 spray/nostril QD (74 mcg daily)
Azelastine HCl/fluticasone propionate	Dymista®	Aqueous spray	137 mcg of azelastine HCl/50 mcg of fluticasone propionate	*≥6 years:* 1 spray per nostril BID (548 mcg Azelastine/200 mcg fluticasone daily)

From Fishbein and Fuleihan [120], with permission
Q every, *QD* once daily, *BID* twice daily, *TID* three times daily
[a]Indicates preparations available over the counter

Immunotherapy

Immunotherapy is a personalized treatment approach to allergic rhinitis involving the repeated administration, either sublingually or subcutaneously, of antigen extract in order to alter the patient's immune response and thus improve their symptoms. Sublingual immunotherapy (SLIT) or subcutaneous immunotherapy (SCIT) is reserved for patients with refractory symptoms despite adequate pharmacologic treatment. In order to utilize immunotherapy, patients must have positive in vitro or skin allergy testing as confirmation of their diagnosis and to initiate treatment. Uniquely, immunotherapy in either form is the only treatment, which may modulate the natural history of the disease and can have lasting effects following the discontinuation of maintenance phase [94–96]. Initially, patients are given regular injections or sublingual preparations of low antigen concentration extracts, and these doses are increased as tolerated until maintenance or a steady state is reached. Patients are then administered maintenance dosing for a variable amount of time, usually between 3 and 5 years.

The initial changes observed are desensitization of mast cells and basophils to allergen followed by changes in T cell and initiation of a T-cell-tolerant state. The mechanism of these changes in T-cell tolerance is largely mediated by IL-10, TGF-ß, and other suppressive mediators ultimately driving the immune system to a normal immune response to allergens. This shifts the balance of the immune system from a TH2-dominated to a TH1-dominated immune response. These T-cell changes are accompanied by modifications in the serum immunoglobulin profiles as well. Although IgE is noted to be transiently increased after initiation of immunotherapy, there is a gradual decrease over the months and years of therapy. Increases in IgG4, a blocking antibody thought to inhibit IgE-mediated inflammation, have been associated with clinical improvement. Immunotherapy-associated increases in IL-10 and T reg cells also modulate the threshold of activation of basophils and mast cells to allergen. There is also a decreased IgE-mediated histamine release [97].

All of the immunologic effects noted in the serum of allergic patients is also supported by clinical observations of decreased inflammation in the nasal mucosa. This

decrease in nasal congestion and inflammatory markers may have a positive impact on sleep, although studies examining these relationships are limited. Several studies assessing efficacy of subcutaneous immunotherapy have demonstrated improvements in quality of life according to the validated Rhinoconjunctivitis Quality of Life Questionnaire [98–100]. These studies did not report sleep domains of the RQLQ separately except in one trial which showed no significant difference in sleep scores between SCIT and placebo [100]. Furthermore, although the sleep domains of RQLQ measure sleep-related symptoms as reported by patients, there have not been robust studies examining the effects of SCIT on sleep-disordered breathing or obstructive sleep apnea. The ability of immunotherapy to alter the natural history of the disease is somewhat mediated by subjects' continued exposure to allergen in order to maintain tolerance. Studies have demonstrated that immunotherapy has the potential to prevent progression of allergic rhinitis to asthma and prevent development of new allergies in monosensitized subjects [94–96, 101].

Subcutaneous immunotherapy was first introduced in 1911 and has been shown to improve the quality of life in patients with allergic rhinitis [102]. Although effective, the onset of action is slow. Improvements in symptoms are noted within 12 weeks of therapy and continue to increase over the first 1–2 years. SCIT is usually administered between 3 and 5 years, and several studies have shown persistent benefit for years following discontinuation of SCIT [94, 96]. These findings as well as persistent decreases in late skin response and IL-4 mRNA expression 3 years after cessation lend support to the theory that immunotherapy can alter the natural history of allergic rhinitis [103, 104]. Treatments are administered over multiple weekly visits to the office, thus requiring a high degree of patient compliance. In addition, adverse events such as anaphylaxis and death are risks of therapy and thus necessitate a high level of supervision, careful screening of patients and specific identification of targeted antigen. Patients with poorly controlled asthma are excluded from therapy due to these risks. The rates of systemic side effects have been reported to be between 0.06% and 0.9% for subcutaneous immunotherapy. Local side effects include redness and induration at the site of injection, are more common, and can occur in up to 58% of patients [105, 106].

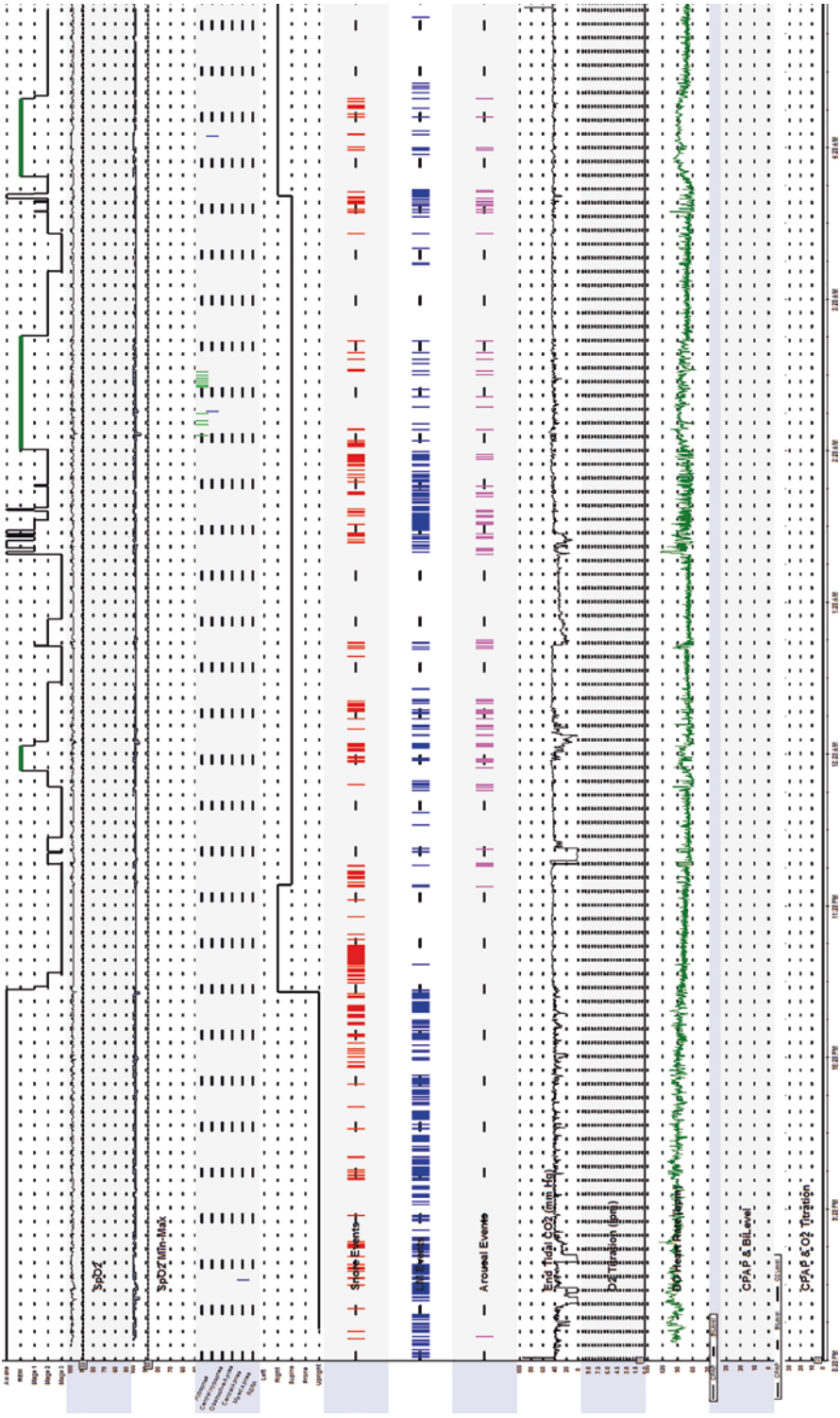
Sublingual immunotherapy (SLIT) is administered utilizing extracts in tablet or liquid form and has similar efficacy as SCIT. SLIT is available for therapy of perennial allergic rhinitis secondary to dust mites as well as formulations for seasonal allergic rhinitis for ragweed and grasses. Data support the use of sublingual preparations for allergic rhinitis as well as allergic ocular symptoms [107–109]. Similar to SCIT, patients undergoing sublingual immunotherapy had significant reduction in symptoms and use of rescue medications compared to placebo. Sleep-specific quality of life indicators have not been extensively studied in this relatively new form of allergic rhinitis therapy; however, two studies comparing SLIT to SCIT in quality of life domains found significant improvement in sleep according to the RQLQ but not in the SLIT group [110]. Another study examining patients undergoing SLIT therapy found significant improvements in quality of life according to the RQLQ and notably within the subdomain of sleep [111]. This study was limited by its small

sample size and lack of a control group. Data regarding the effects of SLIT on sleep-disordered breathing and obstructive sleep apnea is not available as of yet.

SLIT has also been shown to potentially alter the natural history of allergic rhinitis [112, 113]. SLIT has been extensively studied and is considered safe in children and adults [114–116]. The relative ease of administration, especially in children, as well as the ability to be administered at home make SLIT an appealing choice for patients. Some side effects include swelling and itching of the lips and floor of mouth, but there have been reports of anaphylaxis to sublingual preparations of immunotherapy for other allergens including mixes containing multiple allergens [116–118]. There has not been definitive data supporting the superiority of one route versus another in considering immunotherapy although one systematic review found a trend toward superiority of SCIT in controlling symptoms and minimizing rescue medications [119].

Conclusion

Allergic rhinitis is a common chronic condition which affects both children and adults and has a negative impact on quality of life and productivity. The negative impact of allergic rhinitis on sleep is likely multifactorial and as of yet incompletely understood. It is probably related to a combination of increased nasal congestion, ocular itch, and increased inflammatory cytokines. Appropriate management depends on an accurate assessment of the duration, severity, and most bothersome symptoms as well as impact of allergic rhinitis on sleep. Many patients with sleep disturbance will have significant nasal congestion, and thus treatment should be targeted to achieve most relief for this specific symptom. Avoidance of allergens can be difficult to achieve and has limited efficacy in most scenarios. In general, the initial approach to management should include second-generation antihistamines for mild disease and intranasal steroids for moderate to severe disease. Intranasal antihistamines may be effective in decreasing nasal congestion as well as decreasing inflammatory markers, which may also be impacting sleep; however, this is limited by reported side effects of somnolence. The data are mixed in this regard, and if utilized, clinicians should assess side effects of therapy to determine patient's response as well as any new symptoms related to fatigue and somnolence. Evidence for use of intranasal corticosteroids in sleep-disordered breathing and obstructive sleep apnea is robust. In cases where monotherapy does not achieve desired relief, a combination of intranasal steroids and intranasal antihistamines is the most effective combination therapy to date. Other combination therapies that have been shown to be useful include antihistamine-decongestant combination and ipratropium bromide as an additive to target rhinorrhea when it is the dominant symptom. In patients for whom maximal medical therapy fails to alleviate symptoms, immunotherapy should be considered. The advent of sublingual immunotherapy has made this treatment more tolerable to some patients with improved convenience and safety profile. Duration of response


SpO2
SpO2 Min-Max
Stage
Supine
Prone
Upright
Limb Events
Arousal Events
End Tidal CO2 (mm Hg)
Pulse Rate
Desaturation (bpm)
BiPAP Rate
Heart Rate (bpm)
CPAP & BiLevel
CPAP & CO2 Titration

may not be as durable as for subcutaneous immunotherapy, and the range of options is more limited in FDA-approved products. Sleep-related measures have not been as extensively reported after immunotherapy, and this is an area that deserves further research. Allergic rhinitis treatment should be tailored to the particular patient's triggers, quality of life, and symptom burden as well as sensitive to the patient's tolerance of side effects of therapy.

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Part V

Atopic Dermatitis

Sleep-Related Disorders Associated with Atopic Dermatitis

22

Namita Jain, Oriana Sanchez, and Hrayr Attarian

Atopic dermatitis (AD), or eczema, is a chronic inflammatory pruritic skin disorder, with an estimated prevalence of 11% of children and 2–3% of adults in the United States [1]. A majority of those who develop atopic dermatitis will present prior to the age of 5, with up to 50% persisting into adulthood [2]. Disruption of sleep is commonly noted in both children and adults with atopic dermatitis, in part due to nocturnal pruritus and subsequent scratching. As such, the presence of sleep disturbance is incorporated into grading scales for the severity of atopic dermatitis including SCORing Atopic Dermatitis (SCORAD) and the Children's Dermatology Life Quality Index (CDLQI). In children, it is estimated that 60% of those with eczema experience sleep disruption, with up to 83% experiencing sleep disruption during a flare [3]. Adults with atopic dermatitis are more likely to experience shorter sleep duration, difficulty falling asleep, frequent nighttime and early morning awakenings, daytime sleepiness, fatigue, and feeling unrested, in comparison with those without AD [4]. Ultimately, sleep disturbances in patients with atopic dermatitis have been associated with increased risk of mood disorders, poor school or work performance, and impaired performance of instrumental activities of daily living [3, 4].

Sleep is crucial for overall physical and mental health throughout the life span, and poor sleep initiation and frequent prolonged awakenings have an impact in growth [1], daytime behavior, and neurocognitive performance in children [2]. In addition poor parental sleep and associated daytime impairment are described as

N. Jain
Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

O. Sanchez
Northwestern University Feinberg School of Medicine, Chicago, IL, USA

H. Attarian (✉)
Department of Neurology, Sleep Medicine, Northwestern Medicine, Feinberg School of Medicine, Chicago, IL, USA
e-mail: h-attarian@northwestern.edu

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well [5]. Poor sleep in adults presents with a significantly increased risk of cardiovascular and metabolic disease, among other comorbidities [6].

Sleep is composed of two states of being non-rapid eye movement (NREM) sleep and rapid eye movement (REM or stage R) [7]. Healthy adult sleep starts with NREM 1 (N1) that makes up about 5% of the total sleep time (TST). N2 sleep follows, and it makes up of about 50% of normal TST. N3 or slow-wave sleep makes up 20–25% of TST, and stage R makes up another 20–25% of TST [8]. Over the years only a small number of research projects have tried to establish a relationship between sleep disturbances and allergic disease. Below it is provided a brief description of the sleep disorders associated with AD.

Insomnia

Insomnia is defined as a persistent difficulty with sleep initiation, duration, consolidation, or quality, with associated daytime dysfunction, that occurs despite adequate opportunity and circumstances for sleep. Behavioral insomnia occurs in 10–30% of children, with lower rates in adolescents. It can exist as a primary sleep disorder or as a secondary form of sleep disturbance related to an underlying condition. In people with some type of nocturnal discomfort such as pruritus, insomnia occurs at a higher prevalence [5].

Chronic insomnia disorder is diagnosed when the sleep symptoms are persistent for over 3 months independent of the associated in chronic medical or psychiatric disorder's response to treatment. Among children, insomnia can manifest as daytime fatigue, depressed mood, irritability, cognitive impairment, behavioral changes, and impaired academic performance. Adults with chronic insomnia can present with physical symptoms like muscle tension, palpitations, or headache and have reduced quality of life. In severe cases, there is increased risk for work-site accidents as well as psychiatric and cardiovascular disorders [5].

Bouts of scratching due to atopic dermatitis during NREM sleep occurred more frequently in stages N1 and N2 than in stage N3. This pattern is similar in different skin conditions associated with pruritus and appears to be related to sleep stages physiology rather than to the skin diseases themselves [8]. There also appears to be circadian rhythm to this pattern, with the peak of awakenings/scratch ~3 hours after sleep onset [9].

Results from different studies of various methodology, summarized in Table 22.1, show that sleep in children with eczema is characterized by frequent and prolonged awakenings, longer REM onset latency, higher percentage of stage N3 sleep, longer wake after sleep onset (WASO), and a lower subcortical arousal index than controls [3]. In some cases, this seems to be related to deficits in thermoregulatory mechanism [10]. Nevertheless, total sleep time (TST) and sleep stage distribution are similar between eczematous and control children, probably due to a low scratching related arousal index. For important polysomnographic definitions (Table 22.2) [3, 5].

Table 22.1 Atopic dermatitis and sleep disturbances

Title, authors, and year	Population	Results
Sleep disturbance in children with moderate/severe atopic dermatitis: a case-control study (Fishbein et al., 2018, [10])	19 children with atopic dermatitis and 19 controls, ages 6–17 years old	Children with moderate/severe atopic dermatitis had ~103 minutes of wake after sleep onset as compared to 50 minutes in controls, measured on actigraphy. Bedtime and waketime were similar. Disease severity correlated with sleep disturbance
Sleep-related disorders in Latin-American children with atopic dermatitis: a case-control study (Urrutia-Pereira et al., 2017, [11])	340 children with atopic dermatitis and 454 controls, ages range 4–10 years old from nine countries in Latin America	Except for sleep duration, there was a significant Spearman's correlation index for bedtime resistance, sleep anxiety, night awakening, parasomnias, sleep-disordered breathing, daytime sleepiness, and total
Thermoregulation, scratch, itch, and sleep deficits in children with eczema (Camfferman et al., 2016, [12])	18 children with eczema and 15 controls (6–16 years)	Children with eczema had longer periods of nocturnal wakefulness and lower distal temperatures than controls. Higher distal temperature was associated with indicators of poor sleep quality, whereas lower distal temperature was related to more scratching during sleep
Sleep and neurocognitive functioning in children with eczema (Camfferman et al., 2013, [13])	21 children with eczema and 20 healthy controls (age range 6–16 years)	Children with eczema had worse sleep quality on both PSG (notably increased nocturnal wakefulness, a higher number of stage shifts and a longer latency to REM onset) and parental report. They also demonstrated significant neurocognitive deficits (especially verbal comprehension, perceptual reasoning, and to a lesser extent working memory) with a composite Full Scale IQ 16 points lower than controls
Burden of sleep and fatigue in US adults with atopic dermatitis (Attarian et al., 2016, [14])	Sample of 5563 adults from the 2005 to 2006 National Health and Nutrition Examination Survey	There was no significant association between having AD and having a diagnosed sleep disorder (10.44% vs. 7.27%). In multivariate regression models controlling for sociodemographic and lifestyle factors, adults with AD had higher odds of sleep disturbances, including shorter sleep duration, trouble falling asleep, and early morning awakenings
Sleep disturbances in adults with eczema are associated with impaired overall health: a US population-based study (Silverberg et al., 2014, [15])	Sample of 34,613 adults from the 2012 National Health Interview Survey	Adults with eczema had a higher 1-year prevalence of fatigue, regular daytime sleepiness, and insomnia compared with those without eczema
Disease severity, scratching, and sleep quality in patients with atopic dermatitis (Bender et al., 2008, [16])	20 adults that were between 18 and 65 years of age and had mild to moderate AD	Decreased sleep efficiency was associated with increasing disease severity, scratching, and IL-6

AD atopic dermatitis, *PSG* polysomnography

Table 22.2 Definitions of polysomnographic parameters

Sleep onset	Time at which sleep first occurs after lights out
Total sleep time	Time from sleep onset to the end of sleep, minus time awake
Sleep efficiency	Percentage of TST divided by total recording time or time in bed
Arousal	Episodes with abrupt changes in EEG frequency lasting more than 3 seconds, terminated by a return to sleep
Subcortical arousal	Episodes with at least 2 changes in non-EEG channels, such as body movement, heart rate, and respirations
Arousal index	Total number of EEG recorded arousals per hour of sleep
Wake after sleep onset	Total time spent awake after the last epoch of sleep

From Camfferman et al. [12], with permission

Sleep-Related Breathing Disorders

Sleep-related breathing disorders are divided into obstructive sleep apnea (OSA) disorders, central sleep apnea disorders, sleep-related hypoventilation disorders, and sleep-related hypoxemia disorder.

OSA is characterized by upper airway narrowing or closure during sleep, while respiratory effort continues [5]. A respiratory event is defined as an apnea when there is a drop in the peak signal excursion by ≥90% of baseline for ≥10 seconds, when using a oronasal thermal sensor; a respiratory event is defined as a hypopnea when there is a drop in the peak signal excursion by ≥30% of baseline, when using nasal pressure transducer or an alternate hypopnea sensor, with a duration of a least 10 seconds. Hypopneas must be associated with one of the following: oxyhemoglobin desaturation ≥3% from baseline or an arousal per the American Academy of Sleep Medicine (AASM). According to the US Centers for Medicare and Medicaid Services (CMD) hypopnea must be associated with an oxyhemoglobin desaturation ≥4% from baseline [17]. These events more frequently occur in stages N1, N2, and R sleep than in stage N3 sleep [5].

OSA presents differently in children, with primarily obstructive hypoventilation, periods of hypercapnia, and much fewer apneas and hypopneas. Events occur predominantly during stage R sleep [5, 18].

OSA in children can lead to complications such as developmental delay, poor school performance, attention deficit hyperactivity disorder, and aggressive behavior. Rarely, cases of severe asphyxial brain damage, seizures, and coma have been reported. Cardiovascular complications include pulmonary hypertension, cor pulmonale, and systemic hypertension [5].

The possible relation between AD and OSA could be due to their shared systemic inflammatory background [18]. The resolution of dyshidrotic eczema previously refractory to steroids has been reported, after treating OSA with continuous positive airway pressure (CPAP) and a reduction of pro-inflammatory cytokines [19].

The association between AD and OSA in adults is stronger than in children. Table 22.3 summarizes these studies. A population-based case-control study reported that the incidences rates for AD in OSA and non-OSA cohorts were 9.81 and 6.21 per 1000 person-years, respectively. OSA patients were 1.5-fold more likely to develop

Table 22.3 Atopic dermatitis, snoring, and OSA

Title, authors, and year	Population	Results
Obstructive sleep apnea and the risk of atopic dermatitis: a population-based case-control study (Tien et al., 2014, [20])	Random sample from Taiwan's National Health Insurance database, with 1222 patients with newly diagnosed OSA were compared with a matched cohort of 18,330 patients without OSA	Patients with OSA were 1.5 times more likely to develop AD than patients without OSA. Males and younger patients with OSA presented a greater hazard risk for AD
Atopy does not affect the frequency of adenotonsillar hypertrophy and sleep apnea in children who snore (Alexopoulos et al., 2014, [21])	855 children with a mean age (±standard deviation) of 6.3 (±2.5) years who were referred for polysomnography and presented with median obstructive apnea-hypopnea index of 2.1 episodes per hour	Eczema did not affect OSA frequency after adjustment for adenoidal and tonsillar hypertrophy, obesity, gender, and age
Snoring and atopic disease: a strong association (Chng et al., 2004, [22])	10,279 preschool and primary school children aged 4–7 years, randomly selected from 115 preschools and 24 primary schools in Singapore	On multivariate logistic regression analysis, snoring was significantly associated with male gender, race, atopy (asthma, allergic rhinitis, or atopic dermatitis), maternal atopy (allergic rhinitis or atopic dermatitis), maternal smoking, and breastfeeding. Atopy was the strongest risk factor for habitual snoring, and the effect was cumulative

OSA obstructive sleep apnea

AD. Subgroup classification showed that males with OSA were 1.53 times more likely to develop AD than males without OSA, after adjusting for confounders. On the other hand, there were no differences in risk for AD among women with and without OSA. The hazard ratio of developing AD in OSA patients was 4.01 in the age group of 0–18, 1.75 for the age group of 19–24 years, 1.53 in the age group 35–49, and 1.22 among those 50 years of age or older. Therefore, individuals who were diagnosed with OSA later in life were at much less of a risk for developing AD [20].

Snoring is a prevalent symptom among children with OSA. Snoring has been significantly associated with obesity, allergic rhinitis, and atopic dermatitis. In a study done to evaluate the prevalence and factors associated with snoring in a cohort of 10,279 children, atopy was the strongest risk factor for habitual snoring [22, 23].

Difficulty breathing during sleep and morning headaches are also commonly reported in patients with OSA [5]. Daytime sleepiness caused by OSA, which is less common in children that in adults, may be aggravated by AD [20].

Narcolepsy

Patients with narcolepsy present primarily with excessive daytime sleepiness and signs of REM-sleep dissociation, the most specific of which is cataplexy. Usually, they do not have problems with sleep onset, but have inability to maintain

continuous sleep. In children it can manifest as excessively long night sleep or as resumption of previously discontinued daytime napping [5].

There is little data regarding an association between narcolepsy and AD, and existent studies show contradictory results. Presence of allergic conditions, such as allergic rhinitis, atopic dermatitis, and asthma, is indicative of a shift to T helper 2 (Th2) cells. Th2 lymphocytes play an important role in the production of pro-inflammatory cytokines and are involved in the enrollment of eosinophils, the primary effector cells in inflammation [24, 25]. A retrospective study that collected data from three different pediatric sleep centers, with a total of 468 pediatric narcolepsy cases, showed increased frequency of allergic conditions indicative of a shift to Th2 balance in 48.7% of narcoleptic patients without cataplexy (narcolepsy type 2), in comparison with 21.1% of narcolepsy patients with cataplexy (narcolepsy type 1), establishing that allergic diseases may dampen the severity of the phenotype in children with narcolepsy and reduce the prevalence of cataplexy [24].

On the other hand, results from a study of 156 patients with narcolepsy reported that the prevalence of comorbid immunopathological diseases is high in narcolepsy, with a significantly more severe presentation of cataplexy. The European Narcolepsy Network Retrospective Database was used as a reference to establish severity of cataplexy. The frequency of cataplexy was assessed using a scale from 1 to 5. Patients were classified into two groups: mild to moderate cataplexy (scores 0, 1, and 2) and severe cataplexy (scores 4 and 5). Those with higher cataplexy scores had more comorbid immunopathological diseases [26].

Parasomnias and Atopic Dermatitis

Parasomnias describe a group of sleep disorders with abnormal behaviors, movements, emotions, perceptions, or dreams that occur while falling asleep, during sleep, or during arousal from sleep. While there are limited data defining the association between parasomnias and atopic dermatitis, there may be an increased prevalence of parasomnias in patients with atopic dermatitis compared to those without the disease [27, 28]. A case-control study comparing 57 children with atopic dermatitis to 37 age-matched controls found that parents of children with AD reported statistically significant more parasomnias (defined by questionnaire items as “wets the bed at night,” “talks during sleep,” and “restless and moves a lot,” “sleep walks”) than parents of children in the control group. The presence of parasomnias was also associated with severity of disease [27].

Restless Legs Syndrome

Restless legs syndrome (RLS), an unpleasant sensation in the legs leading to an urge to move the legs, has also been described with increased frequency in patients with atopic dermatitis. A study of 253 people, 120 with AD, 50 with psoriasis, and 83 controls, found an increased prevalence of RLS in patients with AD compared to

healthy controls, 18% vs. 10.8%, respectively [29]. Similar to other sleep disorders, the prevalence was greater in those with active AD compared to those with inactive disease [28].

Circadian Rhythm Disorders

Circadian rhythm sleep disorders in atopic dermatitis have not been well-defined. Shifts in cortisol peaks/troughs as found in patients with AD may suggest disruption of normal circadian rhythm; however, the clinical significance of such changes and therapies directed at addressing this disturbance is yet to be determined [30, 31].

Sleep Disturbance in Parents of Children with Atopic Dermatitis and Cosleeping

In children with atopic dermatitis, sleep disturbance is not limited to the affected child alone but also extends to parents caring for children with AD. Sleep disturbance seen in parents with children affected by AD includes more frequent sleep disruption in nighttime awakenings, cosleeping, and greater tiredness, which are associated with severity of the child's skin disease [3, 32–34]. Parents may stay awake at night to prevent children from scratching themselves [35]. Chamlin et al. found that parents who reported sleep disturbance from their child's skin disease were more likely to have children with greater severity of disease as measured by a higher SCORAD index score compared to parents who did not report sleep disturbance. The most important predictor of parental sleep disturbance was the presence of sleep disturbance in the child [34]. The time that parents are kept awake at night has been investigated in small studies, with Moore et al. estimating that mothers who have children with moderate to severe AD lose 39 minutes and fathers 45 minutes nightly [33].

Cosleeping

Cosleeping of children with AD with parents can occur commonly in patients with active disease. Cosleeping was reported by 30% of parents with children with active disease by Chamlin et al., compared to a national estimated average of approximately 13 percent [34]. A majority of these parents also reported that they were bothered by the cosleeping. Again, prevalence of cosleeping was related to severity of disease. Parents who reported cosleeping and parents who reported being bothered by cosleeping had children with higher mean SCORAD index scores than parents who did not report cosleeping or being bothered by cosleeping [34]. Parents may engage in cosleeping as a method to prevent the child from awakening from their disease [35].

Social Impact of Sleep Disturbance Due to Atopic Dermatitis

The impact of sleep disturbance secondary to atopic dermatitis extends broadly to an increased risk for mood disorders, functional impairment from daytime fatigue leading to poor school or work performance, and overall worsened quality of life [3, 14, 15].

Silverberg et al. estimate that the 1-year prevalence of fatigue is over 30% and daytime sleepiness of over 25% in adults with AD [15]. Atopic dermatitis associated with fatigue can lead to decreased ability to perform instrumental activities of daily living (IADLs). Multivariate analysis of NHANES data suggest that when tired, AD is associated with difficulty in concentrating, remembering, eating, performing hobbies, and doing finances [14].

Health Outcomes

Sleep disruption in atopic dermatitis may also be associated with overall poorer health status compared to either AD or sleep disruption alone. In a cross-sectional data analysis from the 2012 National Health Interview Survey including over 3000 individuals, interactions were identified between those with atopic dermatitis and fatigue/sleep disturbance, poorer overall health status, increased number of sick days and missed work days, and increased number of doctor visits [15].

Quality of Life

Most significantly, sleep disturbance in atopic dermatitis affects quality of life in both children and adults. In children with AD, those who reported having their happiness be affected by their skin condition had an increased odds of experiencing sleep disturbance than those who reported their happiness was never affected by their skin condition [34]. Similarly, parents whose happiness was affected by the child's skin condition were more likely to report their child experienced sleep disturbance [34]. Poor sleep is considered among the top two contributing factors (along with pruritus) in reduction of quality of life among children and adults with affected children [35–37].

Treatment

There are limited studies evaluating treatment of sleep disorders in the setting of atopic dermatitis. Leo et al. studied topical treatment of atopic dermatitis using pimecrolimus (topical calcineurin inhibitor) 1% cream and sleep disturbance in 19 children. A trend toward improved sleep in children who had been treated with pimecrolimus was found; however, this finding was not statistically significant [38]. In 265 children, treatment using methylprednisolone aceponate 0.1% ointment was

compared to tacrolimus 0.3% ointment and found to have greater gains in sleep quality than tacrolimus [39].

Treatment focused on pruritus associated with atopic dermatitis is the primary pharmacologic intervention for treatment of sleep disturbance. First-generation H_1 antagonists, such as hydroxyzine, are commonly used as they cross the blood-brain barrier and affect arousal as well as block peripheral inflammatory effects of histamine [40]. Other sedating agents such as tricyclic antidepressants, notably doxepin, may also be used because of their H_1 antagonist properties [40].

Summary

As discussed above, atopic dermatitis is associated with a various number of sleep disturbances. As sleep disturbances can lead to impaired work and school performance, decreased ability to perform activities of daily living, decreased quality of life, and possibly poorer health outcomes, additional research in addressing sleep in the setting of atopic dermatitis is needed.

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Sleep Disruption in Atopic Dermatitis

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Duri Yun and Lacey L. Kruse

Atopic dermatitis (AD) is a common, chronic relapsing inflammatory skin disease with increasing prevalence, affecting 15–30% of children and 2–10% of adults [1]. The prevalence of AD within the United States is higher in metropolitan areas, in households with an education level greater than high school [2], and in geographic areas with decreased mean humidity and decreased UV indices [3]. The typical distribution of AD varies by age, initially affecting extensor surfaces in infancy and shifting to flexural surfaces with time. AD pathogenesis is multifactorial, but genetic polymorphisms causing an impaired skin barrier are thought to play a crucial role. Other factors in AD pathogenesis include altered innate and adaptive immune responses, genetic predisposition to atopic diathesis, and applied environmental factors. Current evidence supports the role of T_H2 and T_H22 inflammation pathways in the development of atopic dermatitis.

AD can be intensely pruritic, particularly during disease exacerbations [4]. Children with AD have frequent overnight movements, presumably triggered by pruritus and scratching [5, 6]. Sleep disturbance has been reported in 47–60% of patients with AD and increases to 83% during an eczema exacerbation [4, 5]. Interestingly, this sleep disturbance can persist despite clinical disease remission [7]. Poor sleep is a major factor leading to impaired quality of life in AD patients, and excessive tiredness is the highest ranked problem by AD patients' family members [7, 8]. Parents of patients with AD will also report a mean reduction in parental sleep during eczema flares ranging between 0.66 and 2.6 hours per night, compounding the impaired quality of life in AD patients [7].

Atopic dermatitis patients report greater difficulty falling asleep, frequent nighttime awakenings, less total sleep, and greater difficulty awakening for school [9]. A US population study (National Survey of Children's Health) of 79,667 children

D. Yun · L. L. Kruse (✉)
Departments of Pediatrics and Dermatology, Northwestern University Feinberg School of Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: LKruse@luriechildrens.org

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found that 10.8% of children with AD experienced four or more nights of impaired sleep during the week [10]. When sleep disturbance is quantified by nighttime actigraphy, sleep efficiency correlated significantly with body surface area involvement of AD [11]. Indeed, it was found that moderate to severe AD patients have an average of 53 minutes more of nighttime awakenings compared to healthy controls [12]. This sleep disturbance results in significant morbidity, including neurocognitive effects, decreased linear growth, behavioral changes, and overall poor quality of life for AD patients and their families [2, 10]. Due to these concerns, the American Academy of Dermatology has recommended that clinicians routinely ask general questions about itch, sleep, and impact on daily activity [13].

Potential Mechanisms of Sleep Disruption in the Setting of Atopic Dermatitis

Pruritus and Scratching

Greater AD severity is associated with increased pruritus and poorer sleep [7, 8, 14]. However, the underlying pathophysiology of this sleep disruption and pruritus is unclear. One reasonable etiology for sleep disruption lies in the itch-scratch cycle associated with AD. This classic theory of AD-associated sleep disruption proposes that pruritus instigates a scratch response, which leads to inflammation, increased pruritus and scratching, and subsequent sleep interruption. However, several studies have failed to correlate pruritus with the degree of sleep disruption, and additional evidence suggests that the mechanism of sleep disturbance is more complex and more systemic in nature [8, 11, 12, 15, 16].

The mechanism and perception of pruritus are complex and mediated by many factors. Molecular factors include neuropeptide-mediated vasodilation, proteases, kinins, and cytokines [1, 7, 8]. Interleukin-31 (IL-31) is a T-cell-derived cytokine which has been shown to be strongly pruritogenic and is expressed at higher levels in atopic skin compared to patients without AD [17]. Neuronal pathways of pruritus are similarly intricate. It has been shown that patients with AD have alterations in cutaneous neuronal architecture, causing hyperesthesia which can be perceived as itch [18]. The skin of AD patients has increased cutaneous nerve density and elongation of nerve fibers into the stratum corneum, leading to sensory hypersensitivity [19, 20]. This has been demonstrated via neuroselective transcutaneous electrical stimulation studies, in which a stimulus preferentially evokes itch in patients with AD, whereas the same stimulus provokes pain in healthy subjects [21]. This intensified itch perception may be due to a dismantled inhibitory interneuron activity within the spinal cord, which would typically perceive pain in the setting of chronic scratching [18]. Normally, peripheral nerves signaling itch can be attenuated by the central nervous system to control the degree of pruritus sensation by exerting tonic inhibition via the descending noradrenergic system. This noradrenergic system is more active during the day, and therefore the relative loss of tonic inhibition at night

may play a role in the nocturnal worsening of pruritus [18]. Finally, the brain of patients with AD processes itch differently than those without AD. Functional MRI studies have shown that different areas of the brain are activated by histamine iontophoresis in AD patients compared to healthy controls. Cortical areas involved in affect and emotion were also significantly more activated in AD patients compared to controls, and this correlated with AD disease severity [22].

Pruritus and Sleep

While pruritus is known to affect most AD patients [4], the subjective nature of itch can make it difficult to correlate patient-reported pruritus with sleep disturbance. Relying on patient recall of sleep quality is also a limitation in many studies of sleep disturbance in AD [11]. For example, one study showed no significant increase in reported sleep disturbance between AD patients compared to healthy controls; however, when measuring sleep in this same cohort, they reported significantly more arousals in the atopic group [24]. Recall of pruritus is similarly inconsistent: several studies have showed that nocturnal wrist movements in AD patients correlate with clinical scores for AD, but not with reported symptoms of pruritus or sleep loss [12, 16, 23].

Therefore, more objective methods are needed to examine the relationship of AD with pruritus and sleep disturbance. Polysomnography has consistently shown decreased sleep efficiency in AD patients, with sleep quality inversely associated with disease severity [11, 24]. Recently, high-resolution wrist actigraphy has been also used to quantify scratching movements, by using a bi-directional recurrent neural network classifier [11, 25]. This relatively new technique allows for quantification of scratching behaviors, which could potentially be used as a proxy for measuring nighttime pruritus. Scratching is most common in the lighter non-rapid eye movement (REM) stages of sleep [11, 26, 27], and most commonly occurs during sustained wakefulness or in association with arousals [11]. This results in increased sleep fragmentation, reduced sleep efficiency, and less non-rapid eye movement sleep [11, 26, 27].

Although pruritus is one cause of sleep disruption in AD, it does not fully account for the degree of sleep disturbance seen in AD patients. For example, AD patients with no clinical disease activity may continue to have frequent arousals and awakenings [24]. One hypothesis for this phenomenon is that AD patients continue to experience abnormal sensory input and sensations of pruritus despite clinical remission. However, on video polysomnography, most of these awakenings in patients with no active disease are not associated with scratching events [24]. Potential alternative mechanisms of sleep disturbance merit further research.

Not surprisingly, parents of AD patients also have impaired sleep. It has been estimated that parents of children with moderate to severe AD lose 39–45 minutes of sleep per night [28, 29]. Increased eczema severity is associated with greater parental reports of sleep disruption [28, 30–32], daytime sleepiness [31, 32], and lost productivity at work [28, 29, 31–35]. Parental sleep quality worsens

with increasing AD severity [30, 32, 33]. Reduced sleep quality in parents of children with AD is also associated with reduced family quality of life [28, 29, 31–35].

Circadian Rhythm

Sleep and the circadian rhythm maintain a complex relationship that is commonly altered in the setting of AD. The periodic nature of pruritus, with characteristic exacerbation at night, suggests that circadian rhythms play a role in mediating the underlying mechanism of pruritus.

Melatonin, an essential hormone in regulating the circadian rhythm, is expressed in multiple cell lines including lymphocytes and keratinocytes [36]. Melatonin has a sedative effect and may be closely linked to the sleep disruption seen in AD. A study by Schwarz et al. measured levels of melatonin in patients with severe AD every 2 hours and found that 14 of the 18 patients studied had diminished or completely abolished levels of melatonin [37]. Children with AD with higher nocturnal melatonin levels have been reported to have better sleep efficiency, less sleep fragmentation, and milder disease severity. These results suggest a compensatory mechanism of increased melatonin secretion in the setting of AD may be at play, which may be insufficient in those experiencing sleep disruption [14]. Melatonin in allergic disease can be pro-inflammatory [38] further complicating the relationship between melatonin and sleep disturbance in AD.

The skin also maintains a peripheral circadian clock that is under the influence of the central circadian pacemaker orchestrated by the suprachiasmatic nucleus of the anterior hypothalamus [39]. Several variables related to skin barrier function are influenced by this circadian rhythm, including transepidermal water loss (TEWL), skin permeability, skin surface pH, and skin temperature [40]. TEWL and skin permeability are increased in the evening and decreased in morning, suggesting circadian fluctuations in skin barrier function [40]. Patients with AD at baseline have increased TEWL in both lesional and nonlesional skin further exacerbating their risk of exposure to irritants and propensity for atopic flares [41]. Higher TEWL has also been associated with higher itch intensity in AD [26]. Cutaneous blood flow also exhibits circadian rhythms, with increased flow in the afternoon and late evening, and lowest flow in the morning. This increased blood flow increases skin temperature in the evening [40]; this increased temperature may play a role in worsening of itch, as heat can increase the sensation of pruritus in hypersensitive atopic skin [4, 40].

Cytokines and immune cells also exhibit diurnal patterns. Pro-inflammatory cytokines such as IL-1β, IL-2, TNF-α, IFN-γ, and IL-6 have been found to be elevated at night and generally promote sleep, while anti-inflammatory cytokines such as IL-4 and IL-10 levels rise in the morning and can inhibit sleep [42, 43]. It has been postulated that the cyclic patterns of these pro-inflammatory cytokines and T-cell activity might contribute to the nocturnal worsening AD and pruritus. A study by Bender et al. showed that patients with AD who maintained the flux between morning and evening levels of IL-6 have increased sleep efficiency [8, 11]. This

delicate circadian milieu highlights the complexity of the relationship between these pathways of pruritus and sleep disruption.

Growth Implications of Sleep Disruption in the Setting of AD

The chronic inflammatory nature of AD, with associated treatment, impairment on quality of life, and sleep disturbance, has led to concern that AD may impact growth and development [44]. Overall, AD is not associated with short stature; however certain subsets of AD patients have decreased height [45]. Most notably, significant sleep disturbance (0–3 nights of sufficient sleep/week) in AD patients less than 11 years old has been associated with short stature below the fifth percentile [45]. However, aside from those with insufficient sleep, moderate to severe AD patients do not display significant effects on linear growth.

AD has also been associated with obesity in multiple population-based studies [46, 47]. In one study, it was found that AD patients had an increased risk of central obesity and high blood pressure [46]. This is of interest because both risks are independently associated with sleep disruption and should be considered by the managing clinician [48–50]. It has yet to be elucidated if these correlations are a risk factor for AD or an adverse sequela.

Behavioral and Neurocognitive Implications of Sleep Disruption in the Setting of Atopic Dermatitis

Sleep disruption in healthy children has been associated with behavioral issues and neurocognitive performance deficits [51–53]. Similarly, more severely affected AD patients may display similar and additional neurocognitive effects [7].

Behavioral deficits reported in patients with AD have included irritability, aggressive behavior, major discipline problems, and attention deficit/hyperactivity disorder [9, 54]. A cross-sectional study by Romanos et al. showed that atopic eczema and concomitant sleep disturbance have more than 2.5-fold increased risk of being diagnosed as having attention deficit/hyperactivity disorder (ADHD) [55]. A population-based study of 354,416 children age 2–17 years found that children with both severe AD and only 0–3 nights of adequate sleep per week had much higher odds of ADHD at 16.83 (7.02–40.33) compared to each independent factor alone [56]. These studies highlight the importance in screening for associated comorbidities when encountering AD, ADHD, or sleep disturbance in the pediatric population.

Other aspects of neurocognitive function may also be impaired in patients with AD and sleep disruption. A cross-sectional study comparing 21 AD patients to 20 healthy controls demonstrated that AD patients with sleep disruption polysomnography demonstrated significant neurocognitive deficits in verbal comprehension, perceptual reasoning, and to a lesser extent working memory [57]. Patients with AD also scored on average 16 points lower on IQ testing than controls [57]. Interestingly, however, there was a lack of an association with increased sleep fragmentation with

neurocognitive deficits or even parental-reported sleep quality with neurocognitive deficits; the strongest predictor of reduced cognitive performance was eczema severity [57].

Other developmental disorders are also increased in patients with AD and sleep disruption. In the National Survey of Children's Healthy survey in 2007–2008, children with both AD and 0–3 adequate nights of sleep per week had dramatically higher odds of speech disorders of 5.85 (2.72–12.53) compared to either factor alone [58]. Several survey studies have also demonstrated an increased risk of developing epilepsy in AD patients, particularly with severe AD and with increased number of comorbid allergic diseases [59–61]. Interestingly, patients with pediatric epilepsy have been known to present with alterations in their circadian rhythms, which leads to changes in cortical excitability and consequently the expression of seizures [62].

Conclusion

In summary, sleep disruption in the setting of AD is multifactorial. Pruritus and scratching are known contributors to sleep disturbance, but more complex and systemic factors also affect sleep. The complex interactions between cytokines, melatonin, circadian rhythms, and pruritus prime AD skin for exacerbations at night. This leads to significant sleep disturbance and poorer quality of life. AD patients with sleep disturbance may also suffer growth disturbances, behavioral issues, and neurocognitive disorders. Recognizing these significant comorbidities associated with AD and sleep disruption highlights the global burden of this disorder on patients and should be accounted for in clinical management.

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Part VI

Chronic Sinusitis

Sleep Dysregulation in Chronic Rhinosinusitis

24

Mahboobeh Mahdavinia and Anjeni Keswani

Chronic rhinosinusitis (CRS) is a heterogenous disorder characterized by persistent local inflammation of the paranasal sinuses [1]. CRS is diagnosed as the presence of at least two out of four clinical symptoms: anterior or posterior mucopurulent drainage, nasal congestion, facial pain or pressure, and a decreased sense of smell, for greater than 12 consecutive weeks. In addition to clinical characteristics, objective evidence of CRS by nasal endoscopy or radiography, preferably sinus computed tomography, is necessary to confirm the diagnosis.

CRS is divided into two different types: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). Although both of these entities affect the paranasal sinuses, the underlying pathophysiology appears distinct. CRSwNP accounts for about one-third of all CRS cases with the remaining cases are diagnosed as CRSsNP. CRSsNP demonstrates predominantly neutrophilic inflammation, whereas CRSwNP is dominated by eosinophilic inflammation and may be accompanied by asthma and aspirin sensitivity [1].

Up to 16% of the US population is affected by CRS [2]. This leads to a reduction in work productivity and a high financial burden on society [3–5]. Patients with CRS report poor health and quality of life (QOL) measures similar in severity to chronic diseases such as severe asthma and end stage renal disease [6–9]. These declines in QOL have been assumed to be due to sinonasal symptoms; however, complaints of fatigue, difficulty concentrating, and impaired memory/productivity may actually be related to poor sleep quality in CRS [10, 11].

M. Mahdavinia
Allergy and Immunology Division, Department of Internal Medicine, Rush University Medical Center, Chicago, IL, USA

A. Keswani (✉)
Division of Allergy/Immunology, Department of Medicine, GW School of Medicine and Health Sciences, Washington, DC, USA
e-mail: akeswani@mfa.gwu.edu

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In studies of sleep in CRS, 60–75% of people with CRS report poor sleep [12–15]. This is considerably higher than the 8–18% of individuals in the general population who report poor sleep [16]. Sleep disruption in CRS has been linked to impaired cognitive function and depression, and these outcomes, in addition to the sleep dysfunction inherent in CRS, further contribute to the poor QOL in individuals with CRS [13, 17, 18].

While few studies have investigated sleep disruption in CRS, there have been many studies on sleep concerns among patients with allergic rhinitis which showcase the relationship between upper airway inflammation and sleep disturbance [19, 20]. Furthermore, other chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease have also been associated with a high prevalence of sleep disturbance [21, 22]. Systemic inflammation may potentially be a contributor to sleep disruption in chronic diseases, including CRS. Exploration of the epidemiology, pathophysiology, and relationship to treatment may help to answer questions underlying the role of sleep dysfunction in CRS.

Epidemiology of Sleep Disturbances in CRS

A variety of methods have been used to assess the prevalence of sleep disturbances in CRS. Alt et al. demonstrated that 75% of CRS patients had poor sleep quality when using the Pittsburgh Sleep Quality Index (PSQI), a self-reported measure of sleep quality over a 4-week period [12]. The PSQI is based on an 18-item questionnaire with a range of scores between 0 and 21. Individuals are considered to have poor sleep quality if they have a score of 5 or greater [23]. In a study of 268 CRS patients, the mean PSQI score was 9.4, indicating poor sleep quality [12]. There was no difference in sleep quality between CRS with and without nasal polyps [12]. The mean PSQI score for CRS is equivalent to that of individuals with chronic obstructive pulmonary disease [11]. When compared to numerous other chronic diseases, only patients with cirrhosis, chronic back pain, and chronic fatigue syndrome reported worse sleep quality via the PSQI [11]. In further concordance, mean PSQI scores of 9.9 and 10.9 have been reported from CRS cohorts in Utah and Singapore/Ontario, respectively [12, 24, 25].

A study from Taiwan used the Epworth Sleepiness Scale (EPSS), an eight-item questionnaire with scores from 0 to 24, to assess daytime sleepiness in a cohort of 139 CRS patients [15]. 38.1% of these individuals had EPSS scores greater than 10 which is indicative of daytime sleepiness [15]. Using the Basic Nordic Sleep Questionnaire in a Swedish population-based study, Bengtsson et al. demonstrated that sleep problems were 50–90% more common among subjects with CRS compared to those without CRS [14]. Individuals with CRS had a higher likelihood of excessive daytime sleepiness, difficulty inducing sleep, difficulty maintaining sleep, snoring, and early morning awakenings [14].

Risk Factors for Sleep Disruption in CRS

Various risk factors have been proposed to explain the high prevalence of sleep disturbance in CRS. Alt et al. assessed a group of patients with CRS for risk factors associated with sleep disruption [12]. Female gender, depression, and current tobacco smoke use were each independently associated with poor sleep quality in CRS. Increased CRS symptoms and reduced QOL measures via the Sino-Nasal Outcome Test-22 (SNOT-22) and the Rhinosinusitis Disability Index (RSDI) were independently associated with poor sleep quality [12]. SNOT-22 is a validated, standardized questionnaire consisting of 22 items covering 5 main domains: (1) nasal, (2) extra nasal, (3) ear/facial symptoms, (4) psychological, and (5) sleep dysfunction [26]. The RSDI is a 30-item survey assessing the impact of CRS on a patient's physical, emotional, and functional subdomains [12]. While both the QOL assessments contain survey-specific items which pertain to sleep, removal of these sleep-related questions did not change the significant association between poor QOL and poor sleep quality [12]. Jiang et al. also demonstrated a significant correlation between SNOT-22 scores and daytime sleepiness in CRS [15].

In a prospective study of 572 adults with CRS, Ando et al. demonstrated that symptoms of nasal obstruction, anterior nasal drainage, facial pain/pressure, headache, and cough significantly correlated with sleep impairment [27]. This study also found an association between lower polyp scores and sleep disruption. Previous studies have also demonstrated that nasal polyps are associated with a twofold higher risk of sleep disturbance [28]. Allergic rhinitis in CRS has also been found to be a risk factor for impaired sleep quality [14, 27]. However, poor sleep quality in CRS has not been associated with disease severity as measured by nasal endoscopy, computed tomography scores, or olfactory function [12].

Pathophysiology of Sleep Disturbance in CRS

The pathophysiology of sleep dysfunction in CRS is likely multifactorial with nasal obstruction, inflammation, and comorbidities of CRS impacting sleep quality. Inflamed and enlarged nasal turbinates, such as those seen in CRS, result in obstruction in nasal air flow and can lead to sleep disruption [29]. Early studies have demonstrated that complete nasal obstruction in healthy individuals can induce apneic episodes, cortical arousals, and transient hypoxia [30, 31]. In this manner, nasal obstruction may predict sleep-disordered breathing and reduced sleep quality. In patients with rhinitis symptoms, nasal obstruction has been significantly associated with poorer sleep quality [32]. Nasal obstruction has a circadian rhythm as it increases during the night and peaks at 6 am [33]. Additionally, nasal patency is affected by position with the horizontal position having the lowest patency [34]. Thus, nasal obstruction and poor nasal air flow may contribute to sleep-disordered breathing [35].

Inflammation in the nasal passages, beyond anatomic obstruction, may also affect sleep dysfunction. Cytokines and their receptors may play a vital role in sleep

physiology as sleep may be regulated by cytokine signaling. Animal models have shown that interleukin(IL)-1beta and tumor necrosis factor (TNF)-alpha may enhance non-rapid eye movement (REM) sleep and regulate REM sleep as both cytokines can induce sleep [36]. Other studies have shown that the cytokines that are highly upregulated in CRS, including IL-4, IL-13, and transforming growth factor (TGF)-beta, can have an antagonistic effect on IL-1beta and TNF-alpha and decrease sleep [11, 36]. Alt et al. reported a correlation between increased microsomal ribonucleic acid (mRNA) expression of IL-4 and TGF-beta and sleep dysfunction [37]. IL-13 expression was found to be associated with poorer CRS disease severity, decreased QOL, and worse sleep quality [37]. Therefore, the balance of these cytokines may influence sleep quality in CRS.

Comorbid conditions, such as depression and chronic pain, may also influence sleep quality in CRS. Inflammatory cytokines may also play a role in these two common comorbidities of CRS. CRS patients have a high prevalence of depression as one-third of CRS patients report symptoms of depression [25]. Additionally, CRS patients often complain of chronic facial pain from their disease. Chronic facial pain and headaches affect sleep initiation and maintenance and have been associated with sleep disruption in CRS [27]. Both depression and chronic pain have been found to be independent risk factors for sleep dysfunction [12, 38].

Effect of Sleep Disruption on QOL and Mental Health in CRS

Sleep dysfunction in CRS has been associated with a decline in QOL, depression, and impairment in cognitive function. Patients with poor sleep quality (defined as a PSQI score > 5) had worse QOL scores measured by the RSDI and worse symptom scores by the SNOT-22 (12). RSDI and SNOT-22 scores correlated positively with total sleep quality scores as well as sleep-related specific variables of sleep latency, sleep duration, sleep efficiency, and daytime function. DeConde et al. demonstrated that CRS patients electing to undergo sinus surgery had significantly higher rates of sleep disruption despite similar sinus- and nasal-specific symptoms compared to patients choosing continued medical management [39]. Consequently, sleep-related symptoms may affect the choice of CRS treatment. The association between QOL and sleep dysfunction in CRS is likely bidirectional where ill health predicts worse sleep and worse sleep may influence QOL [12].

Patients with CRS are at higher risk for depression compared to healthy controls. In a case-control study of depression in CRS patients compared to healthy controls, rates of depression were significantly higher in CRS patients even when controlled for comorbid asthma and allergic rhinitis [25]. Alt et al. demonstrated that a history of depression was associated with poor sleep in CRS [12]. Depression, pain, and sleep dysfunction are interconnected in CRS as well as other inflammatory disorders [40]. This triad is a symptom cluster that affects patients with chronic illnesses and deeply affects QOL. In CRS patients, there was a significant correlation between poor sleep quality, as measures by the PSQI, and pain measures via standardized questionnaires [41]. The correlation with pain measures was found for all three PSQI domains: sleep

quality, sleep latency, and daytime dysfunction [41]. Interestingly, this relationship between pain and sleep dysfunction was only seen in the presence of depression suggesting that depression may be a central factor in this interaction [41].

CRS patients often describe a decrease in cognitive function as demonstrated by complaints of poor concentration or decreased productivity. Overall sleep dysfunction has been linked to cognitive impairment [42]. Soler et al. evaluated 50 CRS patients using the standardized Cognitive Failures Questionnaire (CFQ) and the Fatigue Severity Scale (FSS) [17]. CRS patients scored significantly worse in subjective cognition by total CFQ scores and the FSS [17, 18]. The CFQ scores correlated significantly with sleep quality as measured by the PSQI. In objective assessments of cognitive function, CRS patients also had worse simple reaction time compared to healthy controls [17]. Pro-inflammatory cytokines have been associated with sleep disturbance and cognitive decline [43–45]. As CRS is a chronic inflammatory disorder, pro-inflammatory cytokines may be a link between sleep disturbance and cognitive dysfunction in these patients.

The Role of CRS Treatments in Sleep Dysfunction

There have been numerous studies assessing CRS symptoms after functional endoscopic sinus surgery (FESS), and several of these studies have focused specifically on sleep quality after FESS. In a cohort of 334 CRS patients who underwent FESS, El Rassi et al. found significant improvements in all sleep-related measures by SNOT-22, including difficulty falling asleep, waking up tired, waking up at night, lack of a good night's sleep, and fatigue over the average 14.5-month follow-up period [46]. DeConde et al. also reported a significant improvement in these sleep-related questions of the SNOT-22 in follow-up visits after FESS compared to baseline scores. They assessed the relative change for sleep-related questions in a CRS cohort who underwent FESS and a cohort which was managed medically. Both CRS cohorts improved; however, the surgical cohort had a significantly greater improvement in sleep dysfunction compared to the medically managed cohort [39]. A cohort of 301 CRS patients undergoing FESS were evaluated pre- and postoperatively for sleep dysfunction with a significant improvement found in the PSQI score after FESS in both CRS with and without nasal polyps [13].

A two-center study from Canada and Singapore evaluated sleep disruption in a series of CRS patients without nasal polyps prior to surgery and 6 months after surgery using the EPSS and PSQI [24]. Subjects have significantly improved symptoms after surgery by both of these assessments [24]. Only patients without polyps and without a deviated septum were evaluated to eliminate the confounding factor of improvement in nasal obstruction as a by-product of sinus surgery. In a study of 27 CRS patients with polyps, there was an improvement in mean daytime sleepiness scores and nasal airway resistance following surgery [47]. Sleep-related symptoms from CRS appear to improve after sinus surgery. The reduction in nasal blockage does not appear to fully explain the improvement in sleep dysfunction following sinus surgery, so it is possible that a reduction in inflammatory tissue or an

improvement in other CRS symptoms, such as facial pain and pressure, also contributes to this improvement.

The literature regarding changes in sleep disruption with medical management of CRS is sparse. Studies in chronic rhinitis patients using intranasal corticosteroids have shown improved sleep quality by reducing daytime sleepiness and fatigue as well as significantly lowering the Apnea-Hypopnea Index (AHI) [48]. However, as chronic rhinitis and CRS are distinct disease entities, one can only extrapolate that improvements in sleep quality with intranasal steroids may confer a similar benefit in CRS patients.

Obstructive Sleep Apnea in CRS

Obstructive sleep apnea (OSA) is a common sleep condition which is characterized by a complete or partial collapse of structures in the posterior pharynx during sleep. This results in brief periods of awakening during sleep and episodes of hypoxia [49]. There have been several studies examining the association between OSA and CRS. Studies have shown a varied prevalence of OSA in CRS with a Taiwanese study reporting a prevalence of OSA in 64.7% of CRS patients and another study from the United States, finding a prevalence of 11–15% for physician-diagnosed OSA in CRS [12, 15, 50]. Furthermore, when looking at individuals diagnosed with OSA, they appear to have a high risk of CRS. In a study examining the risk of CRS for patients with OSA, the adjusted hazard ratio for the subsequent development of CRS for patients with OSA was 3.18 (95% confidence interval 2.27~4.45) compared to those without OSA [51]. This hazard ratio was similar for both genders [51].

While the mechanism for the association has not been fully elucidated, the demographics for both OSA and CRS are similar in terms of age distribution, male predilection, and connection to obesity. Obesity has been demonstrated to be a risk factor for both OSA and CRS [52]. Another theory has centered around the potential for bacterial colonization of continuous positive airway pressure (CPAP) machines as a risk factor for CRS developing in OSA patients. However, Chin et al. found no association between sinusitis symptoms as measures by the chronic sinusitis surgery and the presence of bacterial colonization in CPAP machines [53].

A recent study evaluated a large cohort of CRS patients in order to identify risk factors for OSA in CRS. Hui et al. have found that African American patients with CRS are at higher risk for OSA compared with white patients, even after adjusting for other known risk factors such as body mass index, age, and gender, indicating that this patient group should be screened for OSA. Furthermore, OSA was significantly higher in CRSsNP; 12.2% of CRSsNP compared to 8.5% of CRSwNP cases had OSA [50].

Given the high rate of sleep apnea in the CRS population, it is important to evaluate the effect treatment of CRS has on OSA. Two studies have evaluated the role of sinus surgery in the sleep quality and quality of life of CRS patients with comorbid OSA. One study by Alt et al. evaluated 405 CRS patients, out of which 60 (15%) had OSA [13]. Among the 405 CRS patients, 285 participants provided surgery responses

preoperatively and postoperatively over a mean follow-up period of 14 months. Significant postoperative improvement was reported for all disease-specific QOL measures (RSDI and SNOT-22) regardless of comorbid OSA status; however, participants without OSA had significantly greater improvement in PSQI and QOL scores compared to those with OSA [13]. Treatment of CRS did not facilitate as substantial improvement in sleep quality in patients with comorbid OSA compared to those without OSA; therefore, specific strategies to treat OSA in this group are still needed. A second study enrolled 56 patients with CRS and OSA who underwent septoplasty with bilateral inferior turbinate reduction and concurrent FESS. Preoperative and postoperative polysomnography reports, including the AHI, mean and minimum oxygen saturation, sleep efficiency, and sleep staging, were compared. The AHI scores decreased significantly from 33.5 ± 22.0 to 29.4 ± 20.8 after sinonasal surgery [54]. When stratified by OSA severity, AHI scores improved most in the moderate to severe OSA patients, while mild OSA patients did not demonstrate significant improvement [54]. Additionally, the AHI after surgery was still abnormal, well above the normal sleep cutoff of 5.0. Therefore, it is important to recognize that OSA in CRS patients' needs to be evaluated and treated with specific measures targeting the OSA.

Conclusion

Sleep disturbance is a commonly associated symptom in CRS and had led to declines in QOL and cognitive function. Several factors such as nasal airflow disruption and inflammatory cytokines have been implicated in the sleep dysregulation seen in CRS. Medical and surgical treatments do appear to lessen symptoms of sleep disturbance but do not fully treat OSA when it accompanies CRS. Further research is needed into understanding the pathogenesis and optimal treatment for sleep dysfunction in CRS.

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Part VII

Therapies for Sleep and Sleep-Related Breathing Disorders Associated with Atopic Disease

Behavioural Management

25

Charlie Tyack

This chapter is a brief overview of a range of behavioural approaches that can be used to help support people who are experiencing sleep difficulties. The core aspects of these management strategies are the same regardless of the specific health difficulties people might be experiencing. Management of atopy-related symptoms should be optimised in order for behavioural techniques to have the best possible chances of success. There may be situations in which the management of atopy might itself impact on sleep or become associated with getting to sleep, in which case these should be considered carefully in order to give the patient the best chance of independently managing their symptoms, so that in the event of sleep difficulties, they are not reliant on other people for their resolution. Essential foundations of good sleep include a consistent sleep schedule with a regular bedtime routine, which does not change on nonwork or school days, and an age-appropriate bedtime.

Paediatric sleep presentations are related to a range of lifespan phases. Sleep is constantly changing as people move through developmental phases. Whilst total sleep time tends to decrease with age, the range of sleep times that people need stays wide. Thus one adult might need 11 hours of sleep per night to feel well-rested, and another might need just 5. Signs that people are not getting enough sleep include needing over 15 minutes to feel alert after waking, needing to be woken rather than waking spontaneously, falling asleep at inappropriate times, sleeping over 2 hours extra when constraints are removed, and significant mood or behavioural changes after getting more sleep [1, 2].

Behavioural interventions are dependent on engagement: changing habits is a difficult process, as anyone who has attempted to take up a new exercise regime or regularly practise mindfulness will likely be all too aware. A key part of the assessment process should be exploring the goals of the person with sleep difficulties

C. Tyack (✉)
Sleep Medicine Department, Evelina London Children's Hospital, Guy's & St Thomas' NHS Foundation Trust, London, UK
e-mail: Charlie.Tyack@nhs.net
https://www.evelinalondon.nhs.uk/sleep/

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and/or those of their caregivers. Clients and clinicians can approach sleep interventions with divergent assumptions about optimal sleep, and their goals for outcomes can therefore be different. Cultural approaches to "good sleep" and related beliefs influence these goals. Beliefs about the efficacy of medications can also play a big part: some people would rather be *done to* by medication than take an active role in their therapeutic outcomes through behavioural work. This needs exploring if the work is to have a hope of success. Motivational interviewing techniques [3] can help with this exploration, and agreed goals should be SMART (specific, measurable, agreed, realistic, and time-based).

Allergies and Sleep

Allergies can be linked to sleep disorders, as anything that disrupts sleep and leads to arousals, however brief, can significantly reduce sleep quality. It is impossible to cough whilst asleep, so someone with non-optimised asthma who coughs during the night could have many brief micro-arousals of which they are unaware. Likewise, allergic rhinitis and eczema have been shown to affect sleep in proportion to their severity [4].

As can be seen in Figs. 25.1 and 25.2, when allergic rhinitis becomes so severe that the airway becomes obstructed, micro-arousals are possible. Whilst treatments for sleep breathing disorders are primarily via medications and breathing apparatus, behavioural treatments can be used for associated disorders such as NREM parasomnias and in relation to nonadherence with treatments like CPAP.

Behavioural Principles

Behavioural sleep management strategies rely on *behaviourism*, which asserts that behaviour can be observed and categorised, as well as changed using *conditioning*.

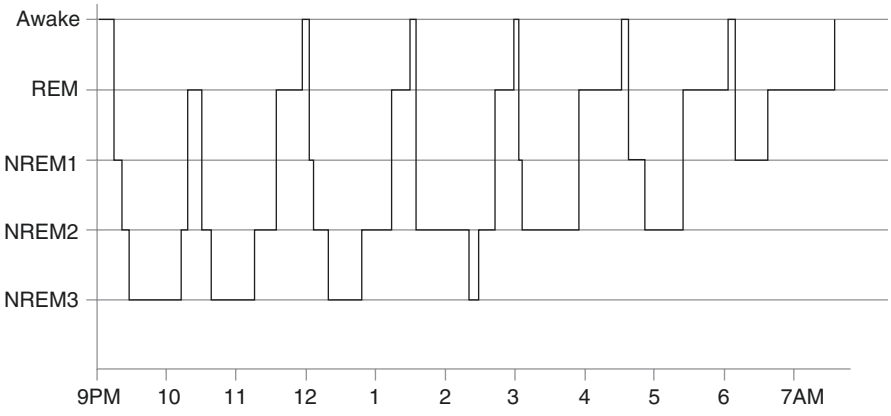


Fig. 25.1 Typical hypnogram

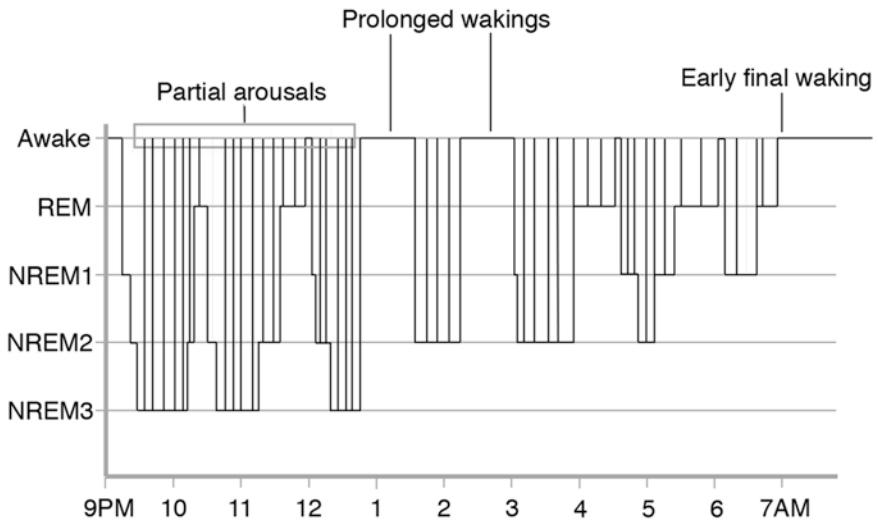


Fig. 25.2 Hypnogram with micro-arousals resulting from allergy symptoms, e.g. airway obstructions from allergic rhinitis

There are two main types of conditioning: *classical* conditioning and *operant* conditioning. Both are pertinent to sleep interventions.

Classical conditioning, also known as Pavlovian conditioning, was made famous by Ivan Pavlov's experiments on dogs. He demonstrated that a dog that salivated (an unconditioned response) on the presentation of food (an unconditioned stimulus) could be trained to salivate (thus making salivation a conditioned response) to a neutral stimulus like the sound of a bell or the illumination of a light. Thus the bell or light eventually triggered a conditioned response of salivation in the absence of food. Importantly from a therapeutic perspective, learned responses can be unlearned, or extinguished, for example, by ringing the bell or lighting the light repeatedly without presenting food. Classical conditioning is especially pertinent to insomnia, sleep onset associations, and bedwetting.

Operant conditioning is concerned with how behaviours can be changed via rewards and punishments. An example of a reward-reinforcing behaviour might be giving a child a treat for helping to tidy up after messy play. The child is likely to want to help tidy up in the future as a result, so the reward deliberately reinforced the wanted behaviour. In some situations, behaviours can be inadvertently reinforced, such as if a parent responds to their child when they are misbehaving in the hope of getting attention. In this situation, even if the parental response is unpleasant (such as shouting), it may still serve as a reward for the child's behaviour, as it had the desired outcome of getting attention and therefore the shouting might lead to the behaviour increasing in frequency. Praise tends to be a powerful reinforcer of behaviour, so mindfully aiming to recognise and praise desired behaviours whilst paying little attention to unwanted behaviours tends to be an effective way to shape

behaviour. Positive reinforcement is the giving of rewards following behaviours, such as a parent giving a child a tablet computer if they start making too much noise. Negative reinforcement is the removal of unwanted stimuli following a given behaviour. This could be parents giving in if a child angrily refuses to take part in chores. In both cases, the reinforcement increases the chance of the behaviour recurring.

An important consideration in relation to reinforcement during operant conditioning is the schedule of reinforcement. Continuous reinforcement is where every incidence of a behaviour is met with the same reward, such as a parent praising their child every time they do their homework without prompting. Intermittent reinforcement is where the reward is given but less frequently. An example of this might be in gambling or fishing, in which the desired prize is obtained relatively sporadically. Intermittent rewards have the capacity to strongly reinforce behaviour. Operant conditioning is especially pertinent in relation to bedtime problems in children, where parents might aim to keep a firm line in relation to certain unwanted behaviours at bedtime but for various reasons such as extreme tiredness on their part might give in on some occasions. These occasional changes might serve as powerful rewards of the child's unwanted bedtime behaviour, even though the rest of the time the parents are working very hard to maintain a consistent schedule.

Good Sleep Habits

The fundamentals of good sleep should be observed by everyone where possible, but are especially important when people have diagnosable sleep disorders. People who struggle with their sleep often develop unhelpful habits out of desperation or simply to pass the time spent awake when they do not want to be and everyone around them is asleep. It is wise to start by revisiting all of these areas in order to make sure they are in place as well as possible. This provides a solid foundation for behavioural interventions.

Attending to the bedroom environment people sleep in is important. Ideally, a bedroom should be like a calm, simple cave, with little in the way of distraction. The optimum temperature for sleep is typically around 18 centigrade (64 Fahrenheit), although this might change according to personal preference. Light levels should be kept to a minimum, with blackout blinds fitted to eliminate external light. If children are fearful of the dark, work to address this may have to be completed before darkness can be fully achieved. If a night light is in use, it should ideally be red, as this has less of a melatonin-suppressant effect than blue. Sound levels should be kept to a minimum. Some people respond well to a constant, low-level sound throughout the night, from a white- or pink-noise generator, a fan, or a radio tuned to static.

In order to promote relaxation, energetic, mentally stimulating activities should not occur immediately before bed. Hunger can disrupt sleep, so a light snack can be eaten before bed. Larger meals should be scheduled earlier in the evening. Anxiety-provoking activities like work or homework should ideally occur earlier in the evening, with a buffer of wind-down time between them and bed. Calming activities should take place later on, such as reading (paper books are generally better than

electronic reading devices), mindfulness, or listening to relaxing music or talking books. Caffeine should be avoided as much as possible, as well as other stimulant drugs, especially in the late afternoon and evening. Electronic devices should be limited in their use, and there should ideally be an electronics curfew of an hour pre bedtime. It has been shown that for adolescents, smartphones in their rooms at night reduce sleep quality and duration and increase sleep onset time, even if they are not being used [5]. It can be helpful to encourage everyone in the house to take part in this, using a central charging location for everyone's devices, so that everyone appreciates how difficult it can be to make this switch and how beneficial it can be. Using dedicated alarm clocks or clock-radios instead of "smart" devices can support this transition.

As bedtime approaches, a set routine can be very helpful, especially with children. This ideally tapers activity and stimulation levels downwards towards bedtime, so that people reach bedtime as relaxed as possible and the stages of the routine cue them into sleep. Stages might include having a bath or shower (a body temperature drop can cue us into sleep), reading something calming or being sung a lullaby for children, putting on pyjamas, brushing teeth, using the toilet, and getting into bed. For people with limited communication abilities, a visual timetable of the routine, or even the actual items associated with each stage arranged in order, can help with their awareness of what to do next and minimise anxiety or confusion. Bed should be a place for sleep: not accessing social media, answering emails, watching TV, or playing games. Getting out of bed as soon as possible after waking supports this. Sleep should not occur in places other than bed. Caregivers should not use bed as a place of punishment.

In order to keep the circadian clock as well entrained as possible, each day should be structured as consistently as possible, with the same wake-up time and (age-appropriate) bedtime, including at the weekend and during holidays. Bright light exposure for at least 20 minutes as soon as possible after waking helps to set waking time and promotes night-time sleep. Physical activity during the day is beneficial and should ideally take place at consistent times, with lower activity levels in the evening. Meals should happen at the same time each day. Artificial light should ideally be dimmer and shifted towards the red-end of the spectrum in the evening and at night.

Assessment

Effective assessment is key to therapeutic interventions in relation to sleep. This allows exploration of the priorities and goals of the patient and/or their family in relation to improving their sleep, which can guide the selection of an appropriate intervention. It should also include establishing and collecting outcomes so that the effectiveness of the intervention can be determined.

Referral letters can be useful, but clinicians' and prospective patients' appraisals of priorities for treatment can differ, so it is important to establish what the client or family would like to address. A clear sense of the profile of the client's

sleep should also be established. A straightforward way to go about this is to start at the time that the person with a sleep difficulty returns home (or starts to prepare for their evening meal if they do not leave the home) and then explore the scheduling: when they have dinner, what happens next, whether there is a consistent wind-down routine after dinner, if they have an electronics curfew and if so how soon before bed, when they go to bed and if they do this alone, and how long it takes to fall asleep. It is important to know if they wake during the night and if so how often and how long it takes them to get back to sleep and if they need anyone else to be present to do so. Their morning wake time is important, and also a sense of how they feel: are they refreshed and ready to get up, or do they still feel tired? How long does it tend to take them to get out of bed? Would they sleep longer if they did not have to get up as early as usual? Do they experience daytime sleepiness? Is this ever so severe that they take naps?

It is important to screen for specific sleep disorders including obstructive sleep apnoea, insomnia, delayed sleep phase syndrome, parasomnias, enuresis, narcolepsy, and restless legs syndrome.

Other areas to cover in assessment include medical history, including medications and specific health conditions that might impact on sleep, such as allergies and asthma. Developmental history is important to capture: conditions such as attention deficit hyperactivity disorder, autistic spectrum condition, and differing levels of intellectual ability can impact on sleep. Asking if the person met all of their developmental milestones when expected can be helpful in exploring this. Mental health and potential stressors should be explored, as anxiety and low mood can affect sleep. Gaining a sense of the person's living environment and its stability can help to explore if the consistency necessary for good sleep is achievable. If the person is dependent on caregivers and spends sleeping in different places, establishing whether sleep routines can be consistent across them is key. Bedroom environment, support resources (including people), diet, and use of caffeine and other drugs are useful to capture. Family history of sleep disorders and mental health difficulties can be enlightening: some sleep disorders can recur across generations, and caregivers experiencing mental health difficulties might find implementation of strategies more challenging.

Objective measurements of sleep can be helpful to establish a baseline and may be repeated later on to measure change. The simplest measure is a sleep diary, kept either by the person with a sleep problem or their caregivers. This involves collecting the same information described earlier about a single night, but over a period of days or weeks.

Diaries can be augmented with actigraphy collected by a watch-sized device worn on the wrist or in the nightclothes of a person who might find it hard to tolerate wearing the watch directly. Analysis of the data an actiwatch collects yields information about movement and light levels, which allows sleep and wake times to be estimated relatively accurately, as well as to gain a sense of the light levels in the bedroom. Adherence to watch-wearing can also communicate a sense of potential engagement in therapeutic work. Sadeh [6] recommended a minimum actigraphy span of 5 days to collect a typical sleep pattern.

Detailed sleep studies such as overnight polysomnography or cardiorespiratory sleep studies can be used to diagnose sleep breathing disorders, periodic limb movement disorders, and explore factors driving hypersomnolence. These can be prone to a "first-night effect" whereby the child does not sleep as they usually do on the first night (which is often the only studied night) owing to the novel sleeping environment. Polysomnography might be followed by a multiple sleep latency test if there are concerns about excessive daytime sleepiness. Questionnaires may also be completed by the person himself or people who see them sleeping in order to gather information about specific symptomatology, such as breathing difficulties or daytime sleepiness.

Once assessment is complete and goals have been collaboratively established, it is important to explore support resources with the individual or family in order to maximise their chances of engagement and success. Resources might be people who act as supporters or coaches to keep them motivated. Exploration of when the best time to start making changes might be is also key, as the individual or family might be about to move or go through a potentially stressful transition. Working out a realistic plan for the implementation of strategies will help them to feel heard and reduce wastage of clinical resources on interventions at times when they are unlikely to be successful. People whose health conditions (including allergies) have meant that they have been in life-threatening health crises in the past might find that they or their caregivers are anxious about them sleeping alone, which could have a significant impact on their realistic therapy goals, and how long caregivers might be prepared to leave them on their own.

Exploring readiness and motivation to change can be achieved through motivational interviewing techniques [3]. It is important to explore these factors with the individual with sleep difficulties where possible, as well as the people who might be supporting them. Motivational interviewing aims to put agency in change in the hands of the person who is experiencing difficulties and/or their caregivers.

Interventions

A wide array of behavioural management strategies can be implemented, depending on the difficulty being addressed and the preferences identified during assessment. Taking a lifespan approach, we shall describe interventions relating to problems in approximate order of when they might be expected to manifest during development.

Sleep Associations and Night Wakings

Young children who tend not to be able to get out of their cot are referred to sleep clinics for difficulties related to repeated night wakings, after which they are unable to return back to sleep independently and therefore require parental presence in order to return to sleep. It is important to note that stigma related to co-sleeping relates to cultural norms: in many cultures, co-sleeping is common until well beyond

infancy. Clinicians should therefore not assume that the goal of any work is to reach independent sleep, unless parents have stated that this is their hope.

Needing parental presence following night wakings tends to be related to the conditions that are present when the child initially goes to sleep (such as being breastfed or rocked) and no longer being present when the child wakes during the night. When this happens, they may summon a parent by crying out. When the parent returns and puts the conditions of initial settling back in place, the child can fall back to sleep and may make it through another sleep cycle before waking again, and the cycle repeats throughout the night. Whilst night wakings are perfectly normal, children with allergies are more prone to discomfort leading to night wakings (Fig. 25.3).

Detailed assessment information is helpful in determining the nature of the night wakings and other factors that might be affecting sleep, including allergies (including possibly as yet unidentified allergies), pain, and illnesses. Treatment for these should be optimised if this has not been done already. Bedtime routine, including timings, should be explored, and the conditions of the initial settling should be established clearly. If bedtime routine and sleep scheduling are not consistent, these should be made as consistent as possible before behavioural interventions are begun. Negotiating how this is to be established is especially crucial in situations where the child sleeps in multiple places, for example, if they sleep at both parents' homes. Sleep associations can be described as "positive", or self-sufficient, and "negative", or dependent on caregiver presence. The intervention strategy tends to focus on moving from a situation in which there are negative associations to one in which the associations no longer require caregiver presence. This starts with the conditions at settling, which usually tend to gradually generalise to all night wakings. Once the child learns to self-soothe, night wakings no longer lead to difficulties.

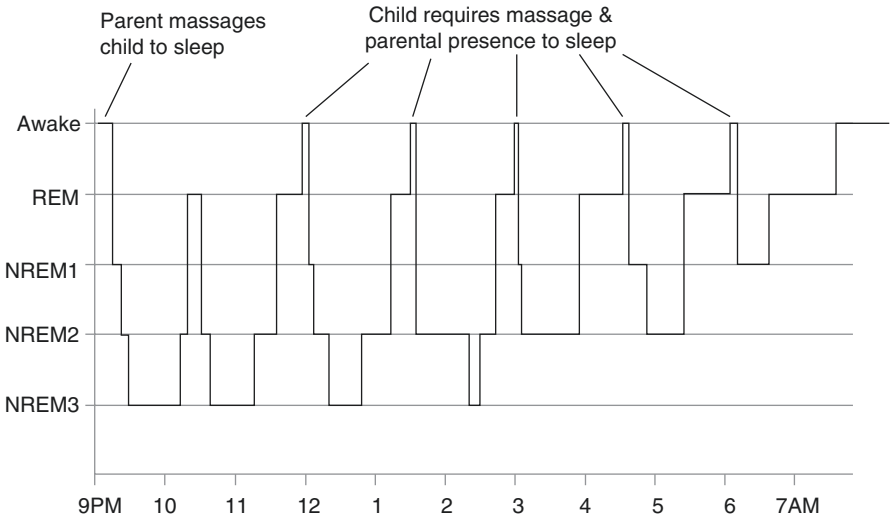


Fig. 25.3 Hypnogram with associations information

The process of making the transition to self-soothing involves extinction, either in a simple form or more gradually. There is evidence to support the effectiveness of these interventions [7]. Concerns in relation to the long-term stress- and attachment-related impacts of behavioural interventions were explored by Gradisar and colleagues [8] who concluded that graduated extinction led to improvements in sleep with no significant impacts in relation to stress or long-term impacts on attachment or children's emotional wellbeing or behaviour. Parenting style and the child's response to interventions dictate the choice of approach, and it is helpful to spend time with parents exploring the balance between approaches that involve shorter episodes of crying but tend to take longer to reach intervention goals and less gradual approaches that can lead to more rapid resolution of difficulties.

Simple Extinction

For families able to consistently implement it, simple extinction offers a rapid resolution to sleep association and night waking difficulties. This can be used with children older than 6 months, once night feedings are no longer needed. Parents tend to report goals being reached in under a week and sometimes in just two nights. The method involves the child being child placed in their cot awake and the caregivers leaving. Caregivers then do not respond to the child's cries at bedtime and during the night, until the child stops crying and learns to go to sleep on their own. Checking should be performed in relation to health concerns (this can be supported via the use of a video intercom to minimise the need for parental presence). It is dependent on the parents not responding to the crying: if they do respond to the cries, they can paradoxically intermittently reinforce the crying, undermining any progress made. Thus it is important to give clear psychoeducation in relation to this, as well as the concept of an "extinction burst": the phenomenon in which the behaviour being extinguished tends to increase in frequency and intensity before eventually decreasing and extinguishing. In some instances, children might vomit, and if the parents discontinue at this point, they might inadvertently reinforce vomiting. In this instance, parents should rapidly replace the bedding and the child's bedclothes, clean them up and give some brief cuddles, and place them back in the cot awake.

Whilst simple extinction tends to be very effective, caregivers might not to want to use this approach. This may be because they find it impossible to hear their child crying without intervening. Children who have had extreme allergic events in the past might evoke a strong response in their caregivers when they seem to be experiencing discomfort, making it especially hard for them to bear. They may also have attempted simple extinction in the past but been unable to resist going in when the child's cries were at a very high intensity, or if the child engaged in a new behaviour, potentially reinforcing louder crying or new behaviours as previously described. It is therefore important to re-establish the principles underpinning extinction methods and explore attitudes to the various approaches.

Gradual Extinction

Whilst it tends to take longer and still tends to involve crying, many parents opt for gradual extinction. There are two main ways to make the approach more gradual. *Controlled checking* entails the caregivers putting the child to bed awake and then leaving them. If they cry, they initially wait for 1 minute, before returning, saying "it's time to sleep", praising them for remaining in bed, making sure the child is safe, and leaving. Some parents opt to offer more soothing at this point, but this can reinforce crying, so the potential cost of doing this (extending the process) should be emphasised. If the child starts crying again, the caregivers should wait for 2 minutes and then repeat the process, increasing to 5 and then extending by 5-minute increments. The maximum recommended span is 50 minutes.

Camping out involves gradually increasing the physical separation between caregivers and child, working towards the agreed goal, which is usually the infant alone in their cot, self-soothing to sleep. The starting point is the current conditions that the caregivers are using to soothe the child to sleep. A series of steps between the current conditions and the goal are established, and once the child becomes calm at each stage, the next stage can be trialled. For example, if a child slept wrapped around a caregiver, the first step might be the unwrapping of one arm, then both, then legs, then gradually increasing distance until the parent can be sat in a chair or sleeping on the floor nearby, then moving gradually away until they reach the door, being outside the door, and then being outside with the door closed if this is part of the goal. If a step causes too much distress, it can be broken down so that the difference from the last stage is smaller, and thus the distress is hopefully manageable by the child-caregiver dyad. We find that the stage of moving outside the door can be a difficult step, so caregivers need encouragement and support at this point, and in some circumstances this stage can be combined with controlled checking to attenuate the shock of the caregiver's absence from the child's perspective. We find that each stage can take up to a week.

Ideally, once the situation at initial settling is adjusted to the goal conditions, the child adapts to this at night wakings. If this does not suffice, caregivers need to implement a strategy of also responding in a minimal, robotic way at night wakings too to minimise any inadvertent reinforcement of behaviours that is occurring.

Older Children

Typically developing older children have the added complication of being more mobile. The techniques described above still apply, but parents may need to implement "rapid return" whereby they robotically turn the child around when they leave their room and guide them back to bed. Some parents describe waking with the child already in bed with them. In this situation, setting up an alerting device such as wind chimes, a passive infra-red sensor linked to a bell, or an intercom can allow parents to wake and return the child to bed, hopefully without too much waking on the part of either party.

Some older children might stall bedtime, with requests for more stories, kisses, drinks, and so on at bedtime. Some parents are more responsive to these requests, and some children are more insistent, which can result in the behaviour being reinforced and perpetuating. Thus, making the cycle and the underpinning reinforcement clear to caregivers is useful, followed by more a more boundaried approach to bedtime. Making sure that a clear wind-down routine is in place can support this, so that children reach their bedtime having been properly cued into sleepiness. In some situations, children have a later time at which they feel sleepy, which may have been behaviourally induced, for example, by allowing them to repeatedly stay up to watch movies or use tablet computers. In this situation, restructuring the pre-bed routine to include wind-down, with at least an hour's electronics curfew before the hoped-for sleep time, will facilitate sleep. Once this is established, gradually "fading" bedtime earlier by 15 minutes per night until the age-appropriate bedtime is reached, and shifting the routine accordingly, will help the family reach their goal.

When children are old enough to conceptualise rewards, the use of "bedtime passes" [9] can be effective. This is where a child is given one or two passes which allow them to get up and trade it with a parent for a small benefit, like a kiss and cuddle, or a small drink of water. If the child does not use the pass all night, then they are allowed to trade it for a better prize the following day. This can be an effective motivator for some children.

Supporting Sleep

The transition to independent sleep is harder for some children and families than others. Various techniques can be used to support the process. Providing some sort of "transitional object", such as a cuddly toy or an item of clothing with a caregiver's scent on it, can be helpful. Associating sleep with smells like lavender and bergamot oil [10] introduced at bedtime and removed in the morning and sounds such as white or pink noise played during sleep [11, 12] can help to support the process.

Some children find the use of clock devices that change colour depending on whether it is time to be awake or asleep helps to reduce the confusion about when it is time to be awake and when it is time to be asleep. Once it is time to be awake, bright light exposure as soon as possible in the morning and preferably some physical activity will help to entrain the child's circadian clock to the desired wake-sleep timing.

Non-REM Parasomnias

Non-REM parasomnias include sleep terrors, confusional arousals, and sleepwalking. The older people are, the more complex the automatic behaviours they tend to be able to engage in whilst they are still in NREM sleep. They tend to occur during slow-wave sleep (N3). They usually occur within the first third of the night, when the N3 cycles occur. Whilst they are upsetting for bystanders, the child usually has no recollection of the event, and if returned to bed and allowed to return to sleep,

they are relatively unaffected. Confusional arousals tend to occur if the child is woken deliberately and involve confusion and sometimes agitation on waking. Sleep terrors involve arousal from N3 with displays of profound fear. Parents often report trying to wake a child from night terrors, as it can be hard to believe that it is not traumatic from the appearance of the event. Sleepwalking involves walking around the room or the home and can include behaviours such as opening doors. Managing risk is therefore paramount in the response to the events.

The array of factors that can increase chances of NREM parasomnia events include inadequate sleep, poor sleep quality, illness, and anxiety. Symptoms of allergies can affect sleep quality [13, 14] and have a link to anxiety [15], so children with allergic conditions have increased risk of parasomnias. Allergy treatment should therefore be optimised.

Once assessment has established the nature of the events, the intervention can be planned. Steps should be taken to optimise sleep as much as possible. This may include work in relation to night wakings as above. If sleep breathing difficulties are identified, these should also be addressed to maximise sleep quality. Ensuring the safety of the child is fundamental, as sleep terrors and sleepwalking can involve leaving the bed and moving around the home. The child is operating on a mental map of the home when this occurs, so as long as nothing has changed, they should be able to navigate the home safely. If something is there that is not there usually, they might trip over it, which is especially dangerous on stairs, for example. Walkways should be kept clear, and windows should be locked shut. Gates can be used to limit access, but it is important that the gates themselves cannot trip the child. Alarms or intercoms can be used to alert parents to wanderings.

Caregivers should be educated about the processes underlying NREM parasomnias, which will help them to understand that it is safe and in their child's interests for them to not intervene when the events happen, beyond making sure their child is safe and guiding them back to their bed. They should avoid waking them as much as possible. If awoken, the experience can be especially confusing and upsetting for the child, which could then feed into future episodes. Likewise, it is important not to attempt to debrief the child the following day, as this could cause unnecessary worry in relation to sleep, further perpetuating the events.

Scheduled Wakings

When episodes happen nightly, they may have a tendency to occur at the same time each night. In this situation "scheduled wakings" [16] can be a very effective intervention. Caregivers keep a diary of the timings of the episodes. This will allow a degree of prediction of the events. Once this has been established, the caregivers should waken the child just to the point at which they show signs of stirring from sleep, by responsiveness or movement, about 20 minutes before the anticipated event. This should be trialled for at least 2 weeks. If the events return after wakings are discontinued, they should be reimplemented until the events resolve.

Rhythmic Movements Related to Sleep

Some children develop a tendency to engage in behaviours to soothe themselves to sleep including headbanging, body rocking, and head rolling. They sometimes manifest during sleep, usually in light NREM stages and sometimes in N3 and REM sleep. They are usually not considered to be pathological, although in some children with neurodevelopmental concerns, the behaviours might have a strength and frequency which means they pose a risk of physical harm to the child. Studies suggest that the majority of infants engage in repetitive movements related to sleep. The most common is body rocking (rocking backwards and forwards whilst on all fours), followed by head rolling (lateral head movements whilst lying down), and headbanging (from lying or sitting into bedding or the headboard or wall). Headbanging children tend to be the most likely to reach specialist sleep services, owing to the caregiver anxiety in relation to risk of injury and possibility of neurodevelopmental concerns it engenders.

Increased frequency of night-time arousals as a result of pain and irritation can increase the chance of rhythmic movements manifesting, so children with allergic conditions have a potentially heightened risk of engaging in them. Parental response, such as intervening to wake the child, can reinforce the behaviours.

The primary treatment for rhythmic movements during sleep is psychoeducation with caregivers about the processes underpinning the movements and letting them know that they are safe and they tend to pass. Making sure the bed is screwed together properly can help keep the child safe, and minimise noise. Guardrails can be installed if there is a risk of the child falling out of bed.

Since parental intervention has a tendency to reinforce the behaviour, parents should be encouraged to stop intervening or attending to the behaviours, even if the child appears to be headbanging with force. Putting padding around the child is unnecessary and might lead to the behaviours being done with added force. Moving the bed away from the surrounding objects and lubricating the bolts can minimise the noise and reduce caregiver alerting. Reviewing sleep scheduling can also help – increasing total sleep time via earlier bedtime or naps can support this. Taking steps to make the bedroom as conducive to sleep as possible are also helpful, such as minimising transient noise and light. Most children discontinue the behaviours by the age of 3, although some people continue to engage in their rhythmic movements into later childhood and occasionally adulthood.

Nocturnal Enuresis/Bedwetting

Nocturnal enuresis is not considered pathological before the age of 5. Once this age has been reached, it has to have been happening at least twice per week for at least 3 months to reach diagnostic criteria. *Primary* enuresis is where a child has never been dry for over 6 months. *Secondary* enuresis is where this has been achieved, but enuresis is now recurring. Enuresis can occur at any sleep stage. Since night-time continence is part of development, it is usually not treated in children under 7 years of age.

As with most sleep conditions, information giving to child and family is the first part of the intervention. This includes normalisation of the behaviour, in case children are feeling ashamed or parents are responding to episodes punitively. Potential secondary triggers should also be addressed, via appropriate medical specialities.

In order to maintain good bladder health, regular urination should be encouraged (every 2 hours or so). Some children might retain fluids at school, thus exacerbating the problem. Children should be encouraged to double-void (normal urination, followed by a wait of at least half a minute, followed by another urination attempt) before bed and if they wake in the night. Increasing fluid throughput during the day, especially by increasing intake in the first half of the day, can improve bladder health and also minimise constipation, which can interact with enuresis. Limiting fluid intake in the evenings should reduce the chance of enuresis.

The most effective treatment for enuresis is the enuresis alarm. These contain a moisture sensor that sounds an alarm when urination occurs. These facilitate classical conditioning, whereby the conditioned stimulus of a full bladder is linked to the unconditioned stimulus of an alarm sound, which triggers the conditioned response of waking. The process usually takes about 4 months and has a success rate of about 40%.

Waking the child at high-risk times during the night can be helpful, although can in itself be frustrating to child and caregivers. Deliberately drinking progressively greater volumes of fluid and extending time between bladder emptying can help to reduce anxiety related to full-bladder sensations and increase bladder capacity. In some cases, rewards can be helpful in encouraging the child to follow good bladder-training habits.

Night-Time Fears and Anxieties

The majority of children experience fears and anxieties at night, which can become more intense as bedtime approaches and in extreme cases lead to bedtime resistance or insomnia. Some families will introduce co-sleeping, either with a sibling or an adult, to address the fear, which can lead to unhelpful negative sleep associations. Fears tend to change depending on age: very young children might fear loud sounds or separation from known caregivers; preschoolers might fear the dark or certain animals, imaginary or otherwise; school can introduce fears and anxieties in relation to social anxiety, tests, being harmed, and anticipated events. Children with allergies might have fears in relation to previous allergic reactions, or of symptom flare-ups, which might become self-fulfilling if their physiological arousal is sufficiently heightened to lead to this. Psychoeducation in relation to allergy management could be helpful in addressing these concerns.

Treatment involves working with the sufferer and their caregivers to facilitate exposure to the fear-inducing stimuli and positively reinforce bravery. If nightmares are occurring, imagery rehearsal and rescripting can be helpful. An example of graduated exposure work could be in relation to fear of the dark. Gamification of the intervention can be helpful and might involve a treasure hunt in the dark with a torch. This entails caregivers secreting objects around the child's room and gradually

increasing the difficulty of the hunt. For children unable to tolerate total darkness, gradually dimming the light level could help to make the steps manageable. A blindfold could be used in a non-dark room to simulate darkness, as a step towards actual darkness. Animal sounds made by parents from another room could be identified by a child in their darkened room, with the time between sounds gradually extended. Hide-and-seek could be carried out in a darkened or pitch-dark home, with parents providing clues if necessary by making sounds.

Simulating camping by temporarily putting up a tent in the child's bedroom can be a fun way to promote exposure. If they have a favourite "brave" character, like a famous explorer, or a superhero, they could try pretending to be them. Relaxation techniques, like deep breathing, or imagery rehearsal, can be especially helpful in managing the physiological fear responses. Caregivers can check on a time basis (every set number of minutes), rather than in response to fears, so that the fear is not inadvertently reinforced. It is important to encourage the child to remain in the fear-provoking location, so that the initial fear subsides, and they do not learn to avoid their bed or room. This may entail caregivers spending time in the room with the child. For older children with fears related to social anxiety or performance, cognitive behavioural therapy techniques might be indicated.

Recurrent nightmares can be addressed by simple reassurance from parents, taking care for this not to become a source of special attention. Gently guiding the child back to bed if they go through to parents can also help to minimise potential secondary gain and reinforcement. If children want the lights on in the aftermath, a dim, reddish nightlight should suffice. Some children have fed back positive results from reimagining the dream and then changing the ending to something more benign. The reimagining is a form of exposure and eliminates the avoidance which can develop when people are especially fearful of something, and changing the ending allows the scary payload of the dream to be neutralised. An example might be for a child who imagines that there is someone in the garden hiding in the bushes with nefarious intentions, who then rehearses the same dream with the alternative version where the person in the garden is a family friend who needs help and culminates with the family helping them. If the dreams recur, the alternative ending rehearsal should be practised as soon as possible.

Gradual exposure might also be used in relation to dream imagery, if possible. An example might be a child with a fear of spiders who has nightmares about them. Exposure might start with photos of spiders and progress towards encountering and potentially handling spiders, so that the fear is faced and eventually subsides. Relaxation techniques such as breathing exercises or progressive muscle relaxation can be combined with the exposure, to help manage the physiological responses.

Insomnia

Insomnia can affect people across the lifespan. It is characterised by difficulty getting to sleep or remaining asleep and sometimes by early morning wakings. It can be triggered for a short period in relation to stressful events or illness. In some instances, it

becomes established for a longer period of time. Diagnostic criteria stipulate that the pattern must have been occurring at least three nights per week for at least 3 months. Whilst it is typically viewed as a night-time problem, it gives rise to difficulties throughout the 24-hour circadian cycle. As insomnia becomes established, several unhelpful associations tend to develop. People tend to spend increasing amounts of their day preoccupied with sleep, whether they will be able to get to sleep, if the amount they get will be enough, how much damage the sleep they have missed out on has done, and so on, which paradoxically reduces their ability to sleep, especially when they worry at bedtime. They also often develop a habit of spending a lot of their time in bed awake, doing a range of things potentially not conducive to sleep.

The first stage of an intervention should be psychoeducation about sleep processes, with a review of circadian rhythms and sleep pressure. There should also be a thorough review of the Good Sleep Habits elaborated earlier in this chapter, as it is likely that some aspects of this could be optimised. In order to gain a clear picture of their current sleep patterns, sleep diaries should be kept for at least a fortnight. This allows average total sleep time to be calculated. It can also help challenge beliefs around how much sleep someone is actually getting. Sometimes, actigraphy can be used to provide an objective measure. People should also be encouraged to become connoisseurs of the difference between being physically tired (a sensation which chronic insomniacs often also feel) and actually being sleepy-tired, with eyes drooping: whilst the former can make one inclined to lie down, it is only the latter which leads to sleep.

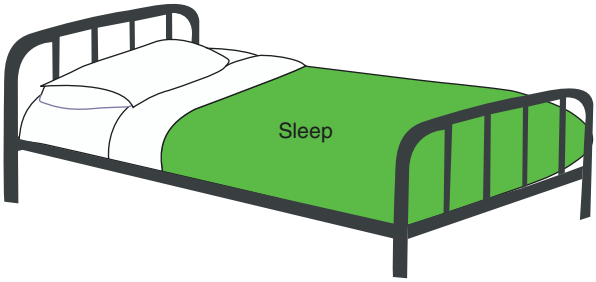
Once the groundwork has been completed, *sleep restriction* can be initiated. This involves setting an anchor wake-up time, to be stuck to as rigidly as possible. Bedtime is set by counting the average total sleep time back from the wake time (stopping at a minimum of 7 hours in children and adolescents, 5 hours in adults). The person is not allowed to go to bed before this time, and if they reach the time and do not feel sleepy, they must stay awake until they do feel sleepy. Napping should be completely avoided. These changes help sleep pressure to build, so that eventually the person with insomnia feels more sleepy at their bed time. It also reduces time spent in bed not sleeping, thereby increasing sleep efficiency. Once sleep has consolidated to the point that sleep efficiency exceeds 85%, the person with insomnia can extend their sleep time in 15-minute increments, waiting until they again exceed 85% sleep efficiency at each stage before extending again, until they reach an age-appropriate total sleep time. Motivation is crucial to this process, so making sure that the person and their supporters are engaged and understand the concepts is key.

Stimulus control entails the person with insomnia making sure that they use their bed and bedroom (as far as possible) solely for sleeping. This means that if they become aware that they have been in bed, not sleeping, for over a quarter of an hour, they are to get out of bed and go somewhere else (ideally another room, but if that is not practicable, then a separate area in their room, screened off from the bed if possible) and do something relatively unstimulating to pass the time until they feel sleepy-tired. They can then return to bed. They should repeat the process as necessary. Over time, this will serve to purify the association between bed and sleep and remove associations with other unhelpful activities, such as worrying about sleeping, doing homework, and using electronics (Figs. 25.4 and 25.5).



Fig. 25.4 Poor stimulus control

Fig. 25.5 Good stimulus control; strong association between bed and sleep



Relaxation techniques, such as imagery rehearsal, square breathing, mindfulness, and progressive muscle relaxation, can all be employed by the person with insomnia to help to manage their physical manifestations of anxiety and tension and to potentially occupy their minds with something other than thoughts related to sleep.

Example Vignette

Tommy, a 6-year-old boy, is referred to the sleep clinic. He is reportedly waking about 2 hours after he goes to sleep each night, shouting, and getting out of bed. His parents try to calm him down by talking to him and putting their hands on him to guide him to bed. When they do this, he seems to grow increasingly upset, lashes out, and sometimes becomes fully alert. Tommy has difficulties settling back to sleep once he wakes. Tommy has eczema, which can be exacerbated when he becomes anxious, and experiences allergic rhinitis from pollen exposure.

Tommy and his parents attend the sleep clinic for assessment. When the history is explored, it is indicative of sleep terrors: Tommy is not actually awake when they take place, and they occur at the same point after Tommy goes to sleep each night.

Tommy's parents state that he snores, and the team order a home oximetry, the results of which are unremarkable. Tommy reports experiencing tickly legs at bedtime and that the sensation is alleviated by moving them. Owing to his eczema, Tommy's parents take turns rubbing lotion onto his skin at bedtime. This helps him to fall asleep and is seen as valuable bonding family time. When his evening routine is explored, there is some inconsistency in timings. Tommy is often given a tablet computer at bedtime as his parents state that this helps him to fall asleep. He is allowed to have this in his room throughout the night. Tommy's room is not fully dark at night, as he is fearful of total darkness. Tommy's room is next to a busy road, used by emergency service vehicles from time to time. A low mood and anxiety screening is conducted, and Tommy is found not to be experiencing anxiety or low mood in excess of clinical thresholds.

The sleep team ask the clinicians managing Tommy's allergy symptoms to review his treatment so that it is optimised. The sleep team also asks his GP to check his blood ferritin level and administer iron supplements as indicated, owing to the symptoms of restless legs which may have been overshadowed by his allergy symptoms. His parents are asked to make his evening timings as consistent as possible. In order to provide a good foundation for sleep, a routine is planned that tapers activity towards bedtime, with a bath shortly before bed. Blackout blinds are fitted to his bedroom windows, and a white-noise maker is used to provide a consistent ambient sound throughout the night and mask the noise of the road.

They are also encouraged to support Tommy to apply his lotions independently, as parental application has become a negative sleep association, potentially keeping him awake after night-time arousals. They are also encouraged to leave him awake to allow him to go to sleep independently. In order to provide a suitable replacement family time activity, the parents are encouraged to schedule an enjoyable alternative activity, and they choose reading together earlier on in the bedtime routine. Tommy is taught relaxation techniques such as breathing exercises to help him manage the physical sensations of anxiety that he experiences. An electronics curfew is implemented, which the parents also abide by to model good sleep practice.

Tommy's parents are given information about sleep terrors, and once they understand that Tommy is actually deeply asleep when they occur and that they are not causing him upset, they are happy to simply ensure that he is safe and wait for them to pass. They stop physically intervening, as they appreciate that it could be perceived as a threat by his sleeping mind and lead to him lashing out or waking. They are given information about scheduled waking techniques in case they are needed. A telephone review is scheduled in a year's time. At review, Tommy is reported to be sleeping well.

Closing Words

This has been a very brief overview of the various behavioural approaches that can be applied to sleep difficulties. For more in-depth information, see Meltzer and McLaughlin Crabtree [17] and Mindell and Owens [18].

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Chronotherapy

26

Laurie A. Manka and Richard J. Martin

Nearly every organ system has been shown to have biologic variations that are related to the sleep-wake cycle and circadian rhythms. This is known as chronobiology. Specifically, chronobiology is the scientific discipline that studies the intrinsic biologic rhythms of all life forms [1]. Many disease states have acrophase, which is the timing of peak incidence of a physiologic process. Both allergic and non-allergic diseases have well-described acrophases [1]. For example, peptic ulcer disease produces its most severe symptoms around 2 am, and myocardial infarction and angina often occur in the early morning hours. Lung function in asthmatics typically worsens at approximately at 4 am (Fig. 26.1). Allergic diseases represent some of the most commonly affected physiologic pathways by chronobiology, and for that reason, there has been ongoing interest in understanding and optimizing therapy for these diseases based on their acrophase. Appropriate timing of therapies for correcting the dysregulation of the specific organ system related to the chronobiology is known as chronotherapy. The chronobiology and chronotherapy (Table 26.1) of several allergic diseases, including asthma, will be reviewed. At the conclusion of the chapter, we'll review different diagnostic studies that are directly affected by the chronobiology of the disease they diagnose.

L. A. Manka (✉)
Division of Pulmonary, Critical Care, and Sleep Medicine, National Jewish Health, Denver, CO, USA
e-mail: mankal@njhealth.org

R. J. Martin
Department of Medicine, National Jewish Health, Denver, CO, USA

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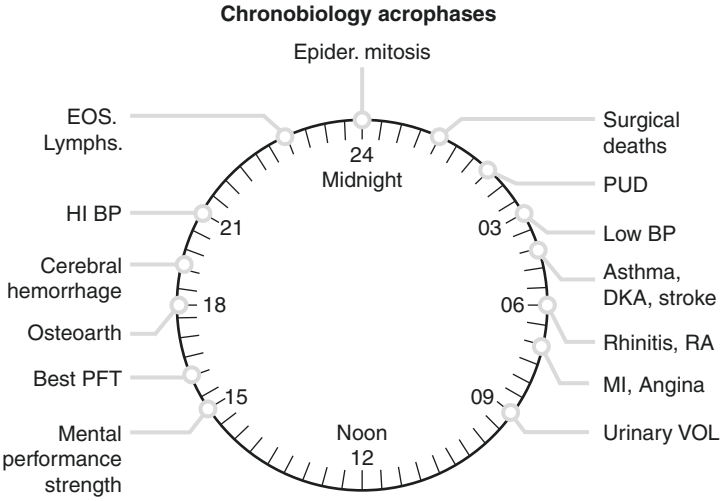


Fig. 26.1 Chronobiology acrophase. Acrophase describes the timing when symptoms related to a particular disease process are at their greatest. Nearly every organ system is affected, including a multitude of allergic diseases. (Adapted from Martin [1], with permission.)

Table 26.1 The chronotherapy of common allergic diseases and frequently used medications in the treatment of those diseases

Allergic disease state	Class of medication	Medication	Suggested time of dosing	References
Asthma				
	Systemic steroids	Prednisone	3 pm	[12]
	Inhaled steroids	Triamcinolone	3–5:30 pm	[13]
		Beclomethasone	5 pm or 10 pm	[14]
		Mometasone	Evening	[15]
	LABA	Salmeterol	Evening	[17]
	Theophylline	Long-acting preparation	7 pm	[18]
	Inhaled anticholinergic	Tiotropium	9 am–1 pm	[20]
	Leukotriene receptor antagonist	Montelukast	Evening	[22]
Allergic rhinitis				
	Antihistamine: second generation	Loratadine	“Bedtime”	[26]
	Leukotriene receptor antagonist	Montelukast	“Bedtime”	[26]
	Inhaled nasal corticosteroid		No known optimal timing	[25]
Atopic dermatitis				
	Antihistamine: first generation	Diphenhydramine	Evening	[27]
	Atypical antidepressant	Mirtazapine	Evening	[27]
Eosinophilic esophagitis/GERD				
	Proton pump inhibitors	Omeprazole	Prior to dinner	[31]

Asthma: Chronobiology

Asthma is a very common disease, affecting nearly 6.2 million children and 24 million adults currently [2]. Nocturnal worsening of asthma has been a well-described phenomenon for centuries, and more recent studies suggest up to 75% of patients with asthma report nocturnal symptoms at least once per week, 64% report awakening at least three times per week, and nearly 40% report nightly awakenings [3]. Despite the frequency of asthma symptoms, the disease is fortunately rarely life-threatening. In a study of 1169 hospital admissions for asthma, only 10 deaths occurred. However, all ten of those deaths occurred between the hours of 12 am and 6 am, suggesting the possibility of significant worsening of asthma in the nocturnal hours [4]. Worsening of symptoms at night has been associated with increased risk of asthma death. In a population-based case-control study over 24 months, authors looked at markers of disease severity, medication use, and use of health resources between those who died of asthma ($N = 42$) compared to both hospital and community controls. They found that those who had died of asthma were more likely to have reported frequently awakening at night with symptoms, among other risk factors [5].

In addition to patient-related symptoms, other makers of disease severity such as airway caliber, measured by peak expiratory flow rates (PEFRs) or forced expiratory volume in 1 second (FEV_1), and bronchial hyperresponsiveness to irritants, such as methacholine and aeroallergens, both follow a circadian rhythm and are most dysfunctional at night [6]. Ballard et al. studied the chronophysiology of alterations of airway caliber. They studied six asthma patients on sequential nights. The first night, the patients were allowed to sleep as they normally would, and the second night, sleep was prevented. Both nights showed an increase in airway resistance and decrease in FEV_1; however, the change was greater the night of sleep [7].

Additionally, airway hyperresponsiveness to aeroallergens fluctuates greatly and worsens at night, based on when the aeroallergen was inhaled. Gervais et al. looked at a small group of four asthmatics. They studied the change in FEV_1, as a marker of bronchial patency, following inhalation of an aeroallergen (house dust) at four time marks throughout the day (8 am, 3 pm, 7 pm, and 11 pm). They found that the drop in FEV_1 was greatest when the exposure occurs at 11 pm (20% decrease) and smallest when the exposure occurred at 3 pm (5% decrease) [8].

Underscoring the significance of circadian variation in asthma symptoms and variability of control is the entity of the late asthmatic response (LAR). There are two types of asthmatic responses a patient can experience when exposed to an aeroallergen that they are sensitized to: immediate and late. The immediate asthmatic response (IAR), which describes the immediate decline in lung function, lasts approximately 30 minutes. The late asthmatic response (LAR) is a second episode of decreased lung function, occurring approximately 3–8 hours later [3]. Mohiuddun and Martin studied the frequency, severity, and duration of the LAR in mild asthmatics. They studied ten asthmatics and exposed them to aeroallergens to which they were sensitized (based on skin prick testing), first at 8 am and then

again at 8 pm. When the aeroallergen was administered at 8 am, all ten subjects noted an IAR and 40% noted an LAR. However, when the aeroallergen challenge was administered at 8 pm, 90% of subjects had an LAR [9]. Additionally, they noted the LAR was noted to be more severe (larger drop in lung function), occurred more quickly, and was longer in duration when the allergen exposure occurred at 8 pm when comparted to 8 am administration [9]. It has been shown that the levels of neutrophils, eosinophils, and lymphocytes vary with the circadian rhythm with the highest levels occurring at night [10], which may help explain the etiology of the increased frequency, duration, and severity of the LAR following evening allergen exposure.

This profound nocturnal worsening of asthma is thought to be driven by multiple physiologic factors including neurohormonal changes, plasma cyclic adenosine monophosphate (cAMP) level, plasma histamine levels, and cholinergic tone [3] (Fig. 26.2).

One of neurohormonal changes that occur in a circadian rhythm is the circulating levels of cortisol. Endogenous cortisol has anti-inflammatory effects on the chronically inflamed airways in asthma. Cortisol peak levels are noted in the morning upon awakening and nadir in the around midnight [11]. Epinephrine is a second hormone that peaks in the afternoon but nadirs in the early morning hours. Asthmatics rely on its direct effect on the beta-2 receptors in the airway smooth muscles to induce bronchodilation. Therefore, low levels of epinephrine may lead to bronchospasm. In addition to the direct stimulation of beta-2 receptors, epinephrine also has an indirect effect on airway patency by regulating other mediators, including cAMP and histamine [11].

Plasma cyclic adenosine monophosphate (cAMP) is an important cell mediator and downstream product in the adenosine triphosphate (ATP) pathway. The ATP pathway is a major pathway in cell responses to a number of neurotransmitters and enzyme signaling. One of the neurotransmitters that utilizes this pathway is epinephrine. cAMP levels are noted to be at their lowest in the early morning, around 4 am [11].

Another important mediator is histamine. Plasma histamine levels, conversely, peak in the early morning hours, around 4 am. The circulating histamine levels are affected by the presence of epinephrine as noted above. Epinephrine levels nadir at 4 am, and therefore, the mast cell stabilizing effect of epinephrine is lost. This allows release of histamine from mast cells and therefore plasma levels of histamine rise. Elevated levels of plasma histamine have been shown to correlate with levels of bronchospasm in asthmatics [11].

Cholinergic tone also affects airway patency in asthmatics. There is increased cholinergic tone at night. Studies have shown that in both asthmatics and controls markers of increased parasympathetic tone increase between the hours of 4 am and 8 am, when compared to noon and 4 pm. The heart rate slows and urinary adrenaline levels nadir in these early morning hours. The airways are exquisitely sensitive to cholinergic tone due to the large number of parasympathetic nerve receptors driving bronchoconstriction, when compared to the relatively sparse number of sympathetic receptors responsible for bronchodilation [12].

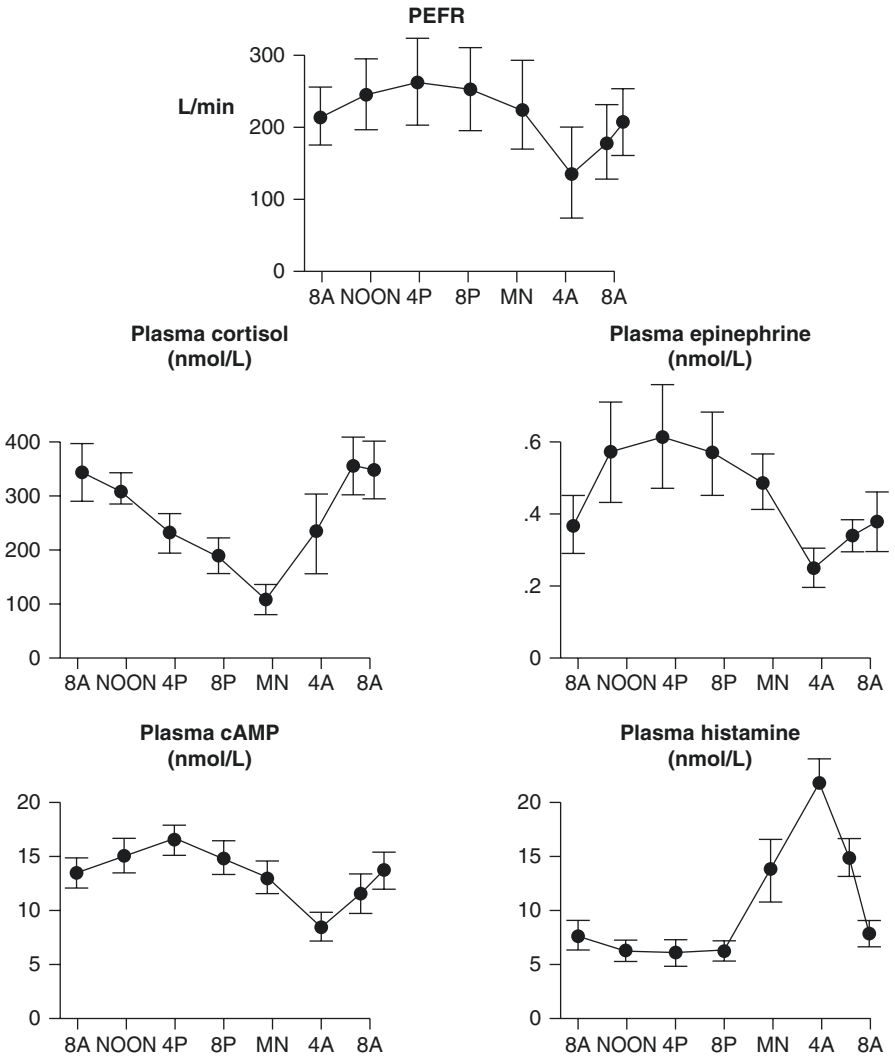


Fig. 26.2 The circadian rhythm variations of underlying neurohormonal and chemical mediators in allergic diseases. The nadir of plasma cortisol, epinephrine, cAMP, and peak of plasma histamine all cause asthma peak expiratory flow rates (PEFRs) to nadir at 4 am. (Adapted from Kraft and Martin [3], with permission.)

Asthma: Chronotherapy

Corticosteroids

Chronotherapy with the use of inhaled corticosteroids in asthma comes from knowledge of oral corticosteroid administration in asthma [1]. In a small study of seven asthmatic patients by Beam et al., once daily dosing at 3 pm of an oral corticosteroid

(prednisone) was found to be superior to traditional 8 am or 8 pm dosing. When dosed with prednisone at 3 pm, the patients had a decreased reduction in FEV_1 overnight when compared to placebo, whereas the 8 am and 8 pm dosing showed no difference in FEV_1 compared to placebo. Additionally, when prednisone was given at 3 pm, the patients actually showed improvement in morning FEV_1 the next day. 3 pm dosing of oral prednisone also resulted in a significant decrease in the number of cellular inflammation recovered bronchoalveolar lavage at 4 am [13].

Catapulted by this discovery with oral corticosteroids, optimal dosing times of inhaled corticosteroids (ICS) became an area of significant clinical interest. In 1997, Pincus et al. showed the optimal once daily dosing of an ICS (triamcinolone acetonide) was between 3 pm and 5:30 pm. Administration of the inhaled ICS once daily in this timeframe showed equal efficacy to the four times daily dose arm in improving PEFRs. Additionally, both the afternoon dosing and QID dosing were superior to once daily morning dosing at 8 am [14]. Prior to this, traditional dosing of ICS was four times daily. Data suggesting once daily or twice daily dosing, when given at the correct time, could not only improve symptoms but also improve medication adherence. An alternate ICS, beclomethasone dipropionate, was looked at to determine if it too, like triamcinolone, was as effective in once daily dosing as opposed to twice daily. The authors did find that beclomethasone had equal efficacy of maintaining mean morning and evening PEFRs, whether administered twice daily (500 μg) or as a single dose (1000 μg) in the late afternoon (5 pm) or at bedtime (10 pm). The authors concluded that a single daily dosing in the late afternoon or evening was an equal alternative to twice daily dosing [15]. Most recently, mometasone furoate showed equal efficacy and safety with once daily dosing in the evening compared to twice daily treatment. In 2001, Noonan et al. showed that inhaled mometasone 200 μg, administered in the evening, was as effective at maintaining FEV_1 readings and morning PEFRs as 400 μg daily dosing in the morning and was superior to 200 μg administered in the morning (although it should be noted that the actual time of ICS administration was not clarified in the publication) [16]. These three studies show a class effect for chronotherapy with ICS. When given in the late afternoon or evening, ICS can provide equal asthma symptom control to higher daily doses administered in the morning or twice daily dosing.

Beta-Agonists

Short-acting beta-agonists (SABAs) provide bronchodilation and symptom relief in asthma. The duration of action of SABAs is approximately 4–6 hours. When taken prior to sleep, this unfortunately leaves most asthmatic patients unprotected during the early morning hours when their asthma is expected to be at its worst [1]. Inhaled long-acting beta-agonists (LABAs) have proven helpful in minimizing nocturnal symptoms. Salmeterol, an inhaled LABA, was the first to come onto the market in the United States. Shortly after it was made available, both high and low doses, 50 μg or 100 μg, respectively, were noted to improve nadir overnight PEFRs as compared to placebo, when administered twice daily. Interestingly, the patients on

the lower dosing (50 μg) arm also reported higher sleep quality, suggesting that high doses of LABA may be difficult to tolerate due to its central nervous system stimulation side effects, particularly at night [17]. Based on these findings, a second study was published in 1994, also looking at salmeterol. This time, twice daily lower dosing (50 μg) was compared with higher dose (100 μg) once daily at night. Outcomes looked at controlling nocturnal asthma symptoms. These authors found that higher dose administered at night was as effective as the lower dose twice a day in averting nighttime asthma symptoms and both dosing regimens showed improved outcomes over placebo [18].

Phosphodiesterase Inhibitors

Theophylline is a complex medicine that is no longer considered first-line or second-line therapy for asthma. The medicine can be difficult to tolerate, and difficult to maintain adequate, yet effective, serum concentrations. Theophylline is a phosphodiesterase inhibitor and mild respiratory stimulant. Theophylline also improves ciliary action and acts as anti-inflammatory agent. Its anti-inflammatory properties help attenuate the worsening nocturnal airway inflammation and edema [1]. It has been shown that achieving higher theophylline serum concentrations at night results in higher awakening FEV_1 measurements. A long-acting (once daily) preparation of theophylline administered at 7 pm (therefore yielding highest serum concentrations in the early morning hours) was shown to be more effective than traditional twice daily dosing of the drug. Although higher serum levels can be difficult to tolerate during the day, there was no evidence of altered sleep latency or efficiency in patients with highest peak serum concentration levels at night in this study [19].

Anticholinergics

Inhaled anticholinergic medications can also be used in the treatment of asthma. It has been shown that vagal tone increases at night and controlling that vagal surge with an anticholinergic medication can provide symptom relief. An early study published in 1988 looked at the effects of anticholinergics in nocturnal asthma. They showed that atropine improved bronchodilation when administered in the early morning hours (4 am) when compared to afternoon (4 pm). The early morning administration of atropine also markedly improved early morning PEFR to values equivalent to daytime levels [20]. The drawback to this was that in order to achieve the greatest benefit from the atropine, it had to be given at 4 am.

Given this improvement in nocturnal symptoms following administration of short-acting atropine, a long-acting inhaled anticholinergic medication, tiotropium bromide, was then studied. A study done by O'Connor et al. showed that administration of tiotropium bromide between the hours of 9 am and 1 pm provided statistically significant protection of airway hyperreactivity to methacholine for 48 hours following medication administration [21]. This study implies that due to long-acting

nature of the medicine, even with morning administration, there is persistent bronchodilation through the nocturnal hours. A subsequent study of inhaled tiotropium bromide in COPD patients showed no significant difference in effect on morning or evening PEFR measurements when tiotropium was administered once daily in the morning versus the evening [22]. Both the earlier asthma study and subsequent COPD study suggest the long-acting duration of tiotropium helps blunt morning nadir PEFR in obstructive lung disease regardless of timing of the dose.

Leukotriene Receptor Antagonists

Montelukast, an oral anti-leukotriene agent, has also shown improvement in nocturnal asthma symptoms when dosed in the evening. Noonan and his colleagues demonstrated that montelukast, when dosed "at bedtime" in adult asthma patients, improved morning FEV_1 and PEFR by 13% and 18%, respectively, when compared to placebo; both were statistically significant [23]. It should be noted that there was no morning dosing of montelukast in this study.

Biologic Agents

There is abundant interest in the treatment of asthma, as well as other allergic diseases including atopic dermatitis and chronic urticaria, using new biologic medications targeting the type 2 (Th2) inflammatory pathway. These medications include an immunoglobulin (Ig) E antibody (omalizumab) and several interleukin (IL) 5 antagonists (mepolizumab, reslizumab, and benralizumab). No study has been done into the optimal timing of these medications. However, the duration of action of these agents is much longer; recommended administration of these agents is every 2–8 weeks. Therefore, they are less likely to be affected by circadian rhythms.

Allergic Rhinitis: Chronobiology

Allergic rhinitis is an inflammatory disease of the upper airway, sinus, and nasal tissue due to hypersensitivity to specific environmental allergens. This results in local inflammation, vasomotor changes, and drainage. Although allergic rhinitis has not been shown to be life-threatening, it can significantly affect quality of life and has been linked to disrupted sleep patterns, daytime fatigue, decreased work performance, irritability, and a depressed mood [24]. Just as in asthma, clinical signs and symptoms of allergic rhinitis, including sneezing, nasal congestion, rhinorrhea, and nasal pruritus, have all been shown to peak in the early morning hours in about 70% of patients with allergic rhinitis [25, 26]. In addition to presence of symptoms, the severity of symptoms can worsen by up to 20% overnight and into the early morning hours [6, 26]. Circadian variation of allergic rhinitis symptoms

are thought to be multifactorial in nature. Upper airway secretions increase due to sleeping position, particularly while supine, and there is increased exposure to allergens like dust mites, molds, and dander to both the upper and lower airway while asleep. Again, similar to asthma chronobiology, circadian rhythms of cortisol, epinephrine, and histamine appear responsible for the increase in nocturnal symptoms related to allergic rhinitis. Additionally, increase in cholinergic activity and vagal tone promotes vasodilation and increased blood flow to the nasal and sinus mucosa, bringing a larger burden of mediators to the nasal and sinus cavities [24].

Allergic Rhinitis: Chronotherapy

H1 Receptor Antagonists

Current drug therapy for allergic rhinitis includes medications such as nasal steroids, leukotriene modifiers, and oral antihistamines. The most information regarding chronotherapy has been published with respect to antihistamines. One study, first published in 1986, evaluated multiple doses and time administrations of an oral H1 receptor antagonist, mequitazine. Participants in this study self-reported the most significant decreases in morning symptoms of allergic rhinitis when two-thirds or all of the dose was administered in the evening around dinner time. It was noted to be least effective when administered in the morning [6]. The differences in daytime and nighttime administration of antihistamines are thought to represent a class effect. Subsequently, an additional second-generation antihistamine, loratadine, was studied. In this study, authors used the disease-specific quality of life instrument most often used with allergic rhinitis, the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), for quantifying symptoms and response. The RQLQ includes effect on sleep as one of its domains. Administration of oral loratadine "at bedtime" not only reduced daytime nasal symptoms but also improved nighttime symptoms, including difficulty going to sleep, nighttime awakenings, and nasal congestion on awakening [27]. However, it should be noted that there was not a daytime administration arm to the study, so a direct comparison could not be made [27].

Leukotriene Receptor Antagonists

Montelukast's effect on nighttime symptoms of allergic rhinitis was also evaluated in the same study as the above noted loratadine [27]. Bedtime administration of montelukast was also was noted to improve quality of life measures for both daytime and nighttime symptoms. Interestingly, the group of patients that received both montelukast and loratadine noted improvement in the quality of life measures in the sleep domain of RQLQ that nearly reached statistical significance when compared to loratadine alone, indicating the combination of the two medications may provide the most symptomatic relief [27].

Intranasal Steroids

Intranasal corticosteroids are considered first-line therapy for moderate to severe seasonal allergic rhinitis; however, no studies have been done to address appropriate timing of nasal steroids. Current investigations of nasal steroids have utilized either morning administration or time of administration was not reported. Intranasal budesonide, flunisolide, fluticasone propionate, mometasone furoate, and triamcinolone acetonide have all been shown to improve nocturnal symptoms and/or sleep quality in patients with allergic rhinitis when compared to placebo, although alternate dosing times have not been tested [26].

Atopic Dermatitis: Chronobiology

Atopic dermatitis is a common dermatologic condition that affects approximately 7.2% of adults in the United States. A large population-based study of adults with atopic dermatitis noted increased fatigue, sleep disturbance, and sleep efficiency. Atopic dermatitis patients were also noted to have more difficulty falling asleep and premature awakening due to nocturnal pruritus compared to controls [28].

Just as in asthma and allergic rhinitis, endogenous corticosteroids and cholinergic surges are thought to play a role as to why pruritus, associated with atopic dermatitis, peaks at night; however, due to the unique nature of the skin as the organ that provides the barrier defense mechanism of the immune system, other mechanisms have also been proposed. Thermoregulation is also thought to affect nocturnal pruritus. Circadian rhythms dictate maximal and minimal core body temperatures. During non-REM sleep, the hypothalamic temperature set point is lowered; therefore, excess heat is released via vasodilation of the peripheral blood vessels. This results in increased blood flow to the skin which consequently can increase itch intensity at night [28]. Also prostaglandins may play a role in nocturnal pruritus. Prostaglandin (PG) D2 and prostaglandin E2 also follow a circadian rhythm. PGD2 and PGE2 levels are elevated at night in normal subjects. They are involved in skin barrier repair after damage from scratching; therefore, any dysregulation of this circadian rhythm could also result in worsening pruritus at night [28].

Atopic Dermatitis: Chronotherapy

Antihistamines

First-generation H1 antihistamines including chlorpheniramine, diphenhydramine, and hydroxyzine are frequently looked to as first-line medications in the treatment of nocturnal pruritus associated with atopic dermatitis due to their sedating side effects, which are maximized when taken in the evening [28]. There are minimal

objective data suggesting that second-generation, or non-sedating, antihistamines relieve nocturnal pruritus in the setting of atopic dermatitis.

Antidepressants (Additional Properties)

Mirtazapine, an atypical antidepressant, has also been reported to reduce nocturnal pruritus in the setting of atopic dermatitis, as well as other inflammatory diseases [28]. The complete mechanism of action mirtazapine is not entirely clear. It has both noradrenergic and serotonergic antagonist effects, which account for its antidepressive properties and also likely act as an anxiolytic in the setting of pruritus. Anxiety can be a strong driver of pruritus, even at night. Mirtazapine also has antihistamine properties, which account for its sedating effects. Evening dosing is recommended for use in both depression and nocturnal pruritus; however, alternate dosing times have not been studied when specifically evaluating nocturnal pruritus associated with atopic dermatitis [28].

Eosinophilic Esophagitis: Chronobiology

Eosinophilic esophagitis (EoE) is an allergic disease of the esophagus which affects as many as 1–5 people out of every 10,000 in the United States [29]. It is characterized by infiltration of eosinophils (>15/high-power field) into the esophagus. The eosinophilic infiltration is driven predominantly by type 2 (Th2) inflammatory response triggered by food and environmental allergens. Presenting symptoms include feeding difficulty and failure to thrive in children. In teenagers and adults, dysphagia and food impaction are more common.

Chronobiology specifically related to EoE has not been studied; however, we do know that gastroesophageal reflux (GER) symptoms often worsen at night. Patients with GER who report a greater severity of heartburn symptoms at night were found to have a higher likelihood of difficulty initiating and maintaining sleep. More frequent nocturnal reflux events and a longer duration of those events were correlated with poor sleep quality and more frequent awakenings [30]. Additionally, patients with nocturnal reflux have shown increased amount of impairment on health-related quality of life surveys, when compared to patients with only daytime heartburn-type symptoms [30].

Chronobiology driving worsening of gastroesophageal reflux symptoms at night is likely related to multiple factors. While supine, whether awake or asleep, there is loss of gravity assisting in esophageal and gastric emptying. There is reduced motility and slowing of esophageal and gastric emptying at night [24]. This is due to reduction in the speed of the migrating motor complexes (MMC) of the gut. The MMC is the motility pacemaker of the gut. The daytime velocity of the MMC has been shown to be more than twice the nocturnal value [31]. There is also cessation of salivation from the oropharynx, which can also delay

transit through the esophagus and lead to increased acidity of the esophagus [32]. Finally, gastric acid secretion peaks at night and specifically between 9 pm and midnight [24, 33].

EoE/GER: Chronotherapy

Proton Pump Inhibitors

Mainstays of therapy in EoE include proton pump inhibitor, swallowed corticosteroids, and diet alteration [29]. Up to one-half of patients with EoE respond to just proton pump inhibitor therapy; this group has been labeled proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE) and represents a subgroup along the EoE spectrum. Chonotherapy in EoE may be most effective in this subgroup, as only PPIs have been evaluated in relation to chronotherapy. Administration of a PPI before dinner has been shown to be more effective in prevention of nocturnal gastric acid breakthrough when compared to administration before breakfast [32]. Hatlebakk and colleagues studied 3 alternate regimens of a proton pump inhibitor, omeprazole, for 7 days in 18 healthy volunteers. They measured intragastric and intraesophageal pH overnight and found that the group of patients receiving pre-dinner dosing of omeprazole had a significant reduction in nocturnal gastric acid levels when compared to the group receiving the morning dose of omeprazole [32]. Interestingly, levels of daytime acidity were not significantly different among the groups.

Chronic Urticaria: Chronobiology and Chronotherapy

Chronic urticaria is a disease characterized by pruritic wheals and angioedema. This can rarely be due to inciting antigens but is most often spontaneous and idiopathic. It is thought to be related to IgE- and non-IgE-mediated release of histamine and other inflammatory mediators from mast cells and basophils. No specific study has been done into the chronobiology of chronic urticaria.

Diagnostic Studies Affected by Chronotherapy

Not only is the treatment of several allergic diseases affected by chronobiology but so is the diagnosis. Clinicians should be aware that many of the frequently used tests for diagnosis of allergic disorders can be altered depending on the time the test was performed. This can lead to misdiagnosis or missed disease severity and subsequently alter therapy and disease course. Diagnostic tests altered by chronobiology include bronchoscopy, peak expiratory flow rates (PEFRs), and skin prick testing.

Bronchoscopy

In a study published in 1990, Martin and Szefler performed evening and early morning bronchoscopy on asthmatics. The asthmatics that were studied were classified in two groups: nocturnal asthmatics, defined as those with a greater than 20% fall in serial PEFRs from bedtime to early morning, and non-nocturnal asthmatics, defined as those with less than a 10% fall in PEFR overnight. They found that there was a significant increase in the total white blood cells, neutrophils, eosinophils, and lymphocytes in the nocturnal asthma group in the early morning bronchoscopy when compared to the non-nocturnal asthmatics [10]. They also noted that this significant change in inflammatory cells within the BAL did not correlate with peripheral blood leukocyte counts, which remained unchanged in the early morning hours [10]. Also found was that the increase in early morning BAL inflammatory cells was not a direct result of bronchoconstriction but more likely related to the circadian changes that occur during sleep [10].

Peak Expiratory Flow Rates

PEFRs in both normal subjects and asthmatics vary based on the circadian rhythm [34]. Although the reported difference in normal subjects from peak to trough was found to be statistically significant (approximately 8%), this is thought not to be clinically significant. Asthmatic patients show the same pattern; however, peak to trough variability can be as much as 50%, with the lowest readings being at approximately 4 am [34]. Furthermore, PEFR measurements even in stable asthmatic outpatients can have large overnight decreases. Bagg and Hughes found that 30 of 40 patients had greater than 20% decrease in overnight PEFR [35]. This has significant implications in management of presumed "stable" asthmatics. Further studies have shown that the changes in PEFR testing in asthmatic subjects are actually not simply a nocturnal phenomenon but are more related to sleep physiology, regardless of time of day in which the patient is sleeping. A study performed in shift workers with asthma, who sleep at night and work during the day, found that the lowest PEFR readings occur upon awakening the morning. Conversely, in those patients who sleep during the day and work at night, PEFR readings are worst upon awakening in the evening [36].

Skin Prick Testing

The greatest response to skin prick testing has been shown to occur the late evening [37]. This has clinical implications because an early morning skin prick test could yield a false-negative response. Had the test been done later in the day, the wheal and flare response may be more pronounced, and the patient may benefit from therapy.

Conclusions

The circadian variation of disease manifestation in allergic diseases is due to the biologic mediators, such as cortisol, epinephrine, and histamine that follow the same circadian rhythm. Alterations in the levels of these mediators manifest as increased symptomatology of allergic diseases most often at night. Because of the prevalence of common allergic diseases, like asthma and allergic rhinitis, and the morbidity associated with frequent symptoms of these disease, much study has gone into the chronotherapy of allergic diseases. Oral corticosteroids, LABAs, ICS, antihistamines, theophylline, leukotriene receptor antagonists, and PPIs all result in better symptom control with appropriate timing of their administration. Less is understood about allergic diseases that are not as prevalent, such as chronic urticaria. As the treatment of allergic disease, particularly severe allergic disease, moves from use of daily medications to use of long-acting biologic medications, the effect of chronobiology on the timing of administration of medications might be less. However, efficacy of timing of administration of biologics can influence responsiveness. This is certainly an area that requires further study.

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Melatonin, Sleep, and Allergy

27

Rui Guan and Roneil G. Malkani

Melatonin has been a remedy for sleep issues since the 1990s [1–3] and gained popularity in the 2000s–2010s to be one of the most popular natural products for adults and children in the USA [4, 5]. Melatonin's popularity for sleep is linked to rising stress in the general population, heightened consumer awareness given its over-the-counter supplement status in North America, and the relatively favorable side effect profile compared to other medications for sleep disorders [6].

Initially associated with skin lightening properties in amphibians at the beginning of the twentieth century [7], melatonin was first isolated in 1958 from the bovine pineal gland [8], and due to its skin lightening properties, it was named melatonin. Over the 1950s–1970s, melatonin was found to be controlled by light, to have neuroendocrine effects [9–12], and to be regulated by circadian rhythm [13]. Bright light exposure suppressed endogenous melatonin secretion in humans [14]. Melatonin also displayed useful antioxidant properties, first in animal models [15–17] and then also in humans, suggesting potential therapeutic uses in cancer [18], critical illness [19], and allergic and atopic diseases [20, 21]. For allergic diseases, melatonin's immunomodulation and antioxidant effects have added importance beyond melatonin's traditional role in sleep. This chapter discusses the effects of melatonin, both endogenously produced and exogenously provided, and its role in sleep and in allergic diseases.

R. Guan
Institute of Neurological Sciences, Prince of Wales Hospital, University of New South Wales, Sydney, NSW, Australia

R. G. Malkani (✉)
Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: r-malkani@northwestern.edu

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Endogenous Melatonin and Physiology

Melatonin is a hormone made primarily by the pinealocytes in the pineal gland in response to the dark phase of the light-dark cycle [22] and by enterochromaffin cells in the gut [23, 24] in response to ingestion of melatonin precursors. Other sources are the retina, skin, platelets, and bone marrow [25–30]. Melatonin synthesis (Fig. 27.1) begins with uptake of tryptophan from the circulation and transformation to serotonin, or 5-hydroxytryptophan (5-HT), which is then converted to melatonin via two sequential enzymatic steps. Serotonin-N-acetyl transferase (5-HT NAT) converts 5-HT to N-acetyl-serotonin in the rate-limiting step to melatonin synthesis, which is then methylated by hydroxyindole-O-methyltransferase to produce melatonin [31].

Melatonin has high lipid and water solubility, which facilitates passage across cell membranes [32] and increases access to various fluid and tissue compartments

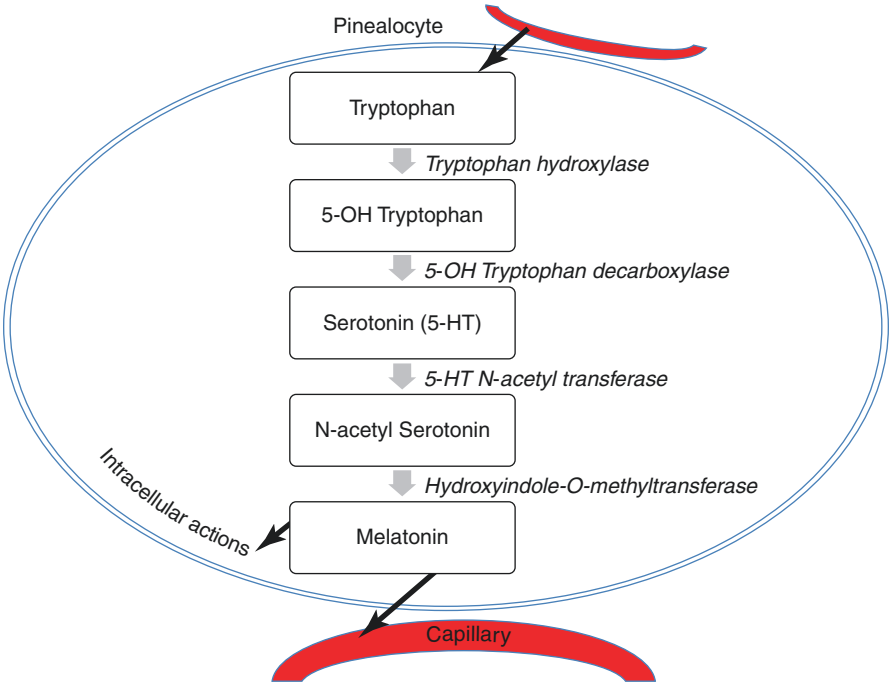


Fig. 27.1 Melatonin synthesis in pinealocytes begins with uptake of tryptophan from the circulation followed by sequential enzymatic steps to form melatonin, which then re-enters the circulation. Tryptophan is first hydroxylated (via tryptophan hydroxylase) to 5-OH tryptophan, which is then decarboxylated (by 5-OH tryptophan decarboxylase) to serotonin. The rate-limiting step is serotonin's N-acetylation (by 5-HT N-acetyl transferase) to N-acetyl serotonin, which then is methylated (by hydroxyindole-O-methyltransferase) to produce melatonin. Due to melatonin's high lipid and water solubility, it passes through the cell membranes to the circulation and can access various fluid and tissue compartments (such as saliva, urine, cerebrospinal fluid, amniotic fluid, and milk)

(saliva, urine, cerebrospinal fluid, preovulatory follicle, semen, amniotic fluid, and milk) [33]. As the pineal gland does not store melatonin, levels of melatonin in various body fluid compartments, such as blood, cerebrospinal fluid, and saliva, reflect pineal activity [34, 35]. Secretion of melatonin occurs at night into cerebrospinal fluid and blood, where it signals the brain and other distant organs leading to effects on sleep and circadian rhythms, among others, like immunomodulation and antioxidant effects.

Circulating melatonin has a half-life of 20–30 min [36]. It is mainly bound to albumin (70%) [37], and it is primary metabolized by the liver (>90%) and then excreted in urine (only ~1% as unchanged melatonin) [38]. Melatonin's hepatic metabolism by cytochrome P-450-mediated 6-hydroxylation and easy passage through various compartments and tissues allow melatonin to be assayed by commercially available methods. The excreted form, 6-sulfatoxymelatonin (aMT6S), can be assayed in the blood, plasma, saliva, and urine [35]. Patients with liver [39] and renal [40] failure can have increases in daytime melatonin and its metabolites as well as blunted melatonin rhythmicity.

Human endogenous melatonin starts to increase around 2 h before the natural sleep onset and peaks around 5 h later [41]. The maximal blood level occurs most commonly between 02:00 and 04:00 and then gradually falls in the second half of the night to daytime levels that are undetectable or low in rested subjects [33, 42]. Nocturnal melatonin production rates are around 100 pg/ml in each melatonin secretory burst to accumulate between 10 and 80 μg per night [43, 44] as estimated from plasma melatonin concentration.

Melatonin secretion occurs in a circadian rhythm [from the Latin circa (approximately) + *diem* (a day)]. Circadian rhythms are endogenous, entrainable rhythms of an organism that can respond to external influences such as light. Many aspects of the body show properties controlled by circadian rhythms. For example, immune cell counts have complex relationships with diurnal and nocturnal levels, and cortisol levels are highest in the biological morning; pruritus in skin conditions is generally increased at night [45]. For more information, please see the chapters about circadian rhythms and chronotherapy.

A key area controlling melatonin secretion is the suprachiasmatic nuclei (SCN), the master circadian clock, located in the hypothalamus. The SCN uses external cues, such as light, melatonin, feeding, and activity to coordinate and reset the timing of the clock. During the circadian day, pinealocytes in the pineal gland sequester serotonin so that it is not available to monoamine oxidase and enzymes in the melatonin synthesis pathway. During the circadian night, postganglionic sympathetic signaling increases to the pineal gland, resulting in release of norepinephrine onto pinealocytes, causing stored serotonin to be accessible for intracellular metabolism, and activation of the enzymes that convert serotonin to melatonin [9, 12, 46]. Pineal melatonin levels rise in the biological night and fall in the biological morning, forming a rhythmic cycle that spans approximately a day.

Melatonin secretion is mediated by a neural pathway involving the retina and SCN, resulting in its circadian control and suppression response to light. Melanopsin-containing photosensitive retinal ganglion cells, responding to light, project via the

retinohypothalamic tract to the SCN [47]. GABAergic neurons in the SCN inhibit neurons of the paraventricular nucleus of the hypothalamus (PVN). The PVN neurons activate preganglionic neurons of the intermediolateral cell column which project to the superior cervical ganglion of the sympathetic chain [48, 49]. Next, the superior cervical ganglion projects postganglionic axons to the pineal gland, where norepinephrine acts via β-1 receptors to increase the activity of the rate-limiting enzyme (5HT-NAT) for melatonin synthesis. This norepinephrine release occurs at night in response to signals from the SCN [46, 50, 51]; in the daytime, norepinephrine release is suppressed by the SCN, resulting in decreased synthesis and release of melatonin [46]. Melatonin feeds back to the SCN, inhibiting its firing, muting the SCN's alerting effects, and resetting the circadian pacemaker [52].

Artificial light at night can suppress melatonin production and secretion, whereby even common household light intensities (50–300 lux) can have a modest suppressive effect [53]. After light exposure for multiple nights, the circadian rhythm as measured by melatonin secretion becomes progressively delayed. Light exposure in the biological morning for several days can advance the circadian rhythm as measured by melatonin secretion [54–56]. In the treatment of circadian rhythm disorders, full-spectrum bright light is usually used, but the most effective wavelengths are in the range of 446–477 nm (blue) [54, 55]. For more information on the application of light and circadian rhythms, please refer to the chronotherapy and phototherapy chapters.

Nocturnal melatonin secretion can also be pharmacologically suppressed by β-1 receptor blockers [57] and the α-2 receptor blocker clonidine [58–60]. Melatonin secretion can be enhanced by drugs that increase synaptic catecholamine availability (e.g., monoamine oxidase inhibitors or tricyclic antidepressants) [61]. Neurotransmitters involved in controlling pineal activity can alter melatonin secretion. In animal models, vasoactive intestinal peptide, pituitary adenylate cyclase-activating peptide and opioids stimulate melatonin secretion, whereas GABA, neuropeptide Y, dopamine, and glutamate inhibit melatonin production [33]. GABA-receptor activation by benzodiazepines and increasing GABAergic tone by valproate reduces melatonin levels at night in humans [62].

Over the life span, melatonin levels change dramatically. Melatonin secretion starts at 3–4 months of life, coinciding with nighttime sleep consolidation [63]. In childhood, rhythmic melatonin production reaches the highest levels at age 3–6 years. The nocturnal peak drops progressively during sexual maturation by 80% to reach adult levels [64]. With aging, besides transiently elevated melatonin levels in menopause [65], the amplitude of the melatonin rhythm progressively dampens, with a tendency to phase-advance, and melatonin levels can be completely abolished in advanced age [66].

The embryo and fetus depend on maternal melatonin, which crosses the placenta. This rhythmic signal helps to synchronize the fetal biological clock [64]. Melatonin concentrations rise in maternal blood in pregnancy to reach a maximum at term [67]. Melatonin in human breast milk displays a circadian rhythm, with highest levels at night and undetectable levels in daytime [68] – this rhythm could communicate time cues and sleep-wake behavior to the breast-fed infants while their own circadian system matures. Given these data, it is important to consider the benefit of darkness for breastfeeding at night because light suppresses melatonin secretion for the mother and the child. Also, it may be important to separate milk collected during the day or

night to feed newborns with the milk corresponding to the appropriate periods, especially when using milk from milk banks. Moreover, synthetic milk formulation may benefit from products with compositions suitable for night versus day to achieve a chronobiological effect on the circadian rhythm in newborns [67]. Thus, adding melatonin, its analogues, or precursors in night milk formulas has had international interest [67, 69–72]. This has shown promise in a double-blind crossover trial with 30 human infants aged 4–20 weeks, whereby sleeping problems were improved by feeding during 06:00–18:00 with day milk containing low tryptophan (1.5 g/100 g protein) and feeding during 18:00–06:00 with night milk containing high tryptophan (3.4 g/100 g protein), in concordance with their environment [73]; the pattern of urinary metabolites of serotonin suggests an increase of serotonin to melatonin synthesis, which may be responsible for the sleep improvements [74].

Melatonin has effects beyond sleep, such as anti-inflammatory effects in the cardiovascular system and decreasing sun damage to the skin, due to its receptors' wide distribution throughout the body. Melatonin receptors are found in the brain, retina, cardiovascular system (ventricular wall of the heart, aorta, coronary and cerebral arteries), liver and gallbladder, duodenal enterocytes, colon, cecum, vermiform appendix, skin, parotid gland, exocrine, pancreas, kidney, immune cells, platelets, brown and white adipocytes, epithelial cells of the prostate and breast, ovary/granulosa cells, myometrium, placenta, and fetal kidney [75, 76]. In the gastrointestinal system, melatonin receptors are most common in jejunal and colonic mucosa [77].

There are multiple melatonin receptor subtypes with different functions. Melatonin receptor type 1 (MT1) is expressed in the SCN, cortex, and skin [77]. MT1 receptors reduce neuronal discharge rate in the SCN and suppress prolactin secretion [78]. Melatonin receptor type 2 (MT2) is expressed in melanocytes and eccrine sweat glands, and in the brain they inhibit GABA-A-related function; MT2 receptors are responsible for the hypnotic, antidepressant, and anxiolytic effects of melatonin [79]. A genetic mouse study showed that MT1 knockout mice had decreased stage REM sleep and MT2 knockout mice had decreased NREM sleep [80]. Melatonin receptor type 3 (MT3) is found systemically (liver, kidney, heart, lung, intestines, muscle, and brown fat); its melatonin binding site is an enzyme, quinone reductase 2, which protects against oxidative stress [81–83]. MT1, MT2, and MT3 are membrane receptors and predominantly located in the central nervous system with associated downstream effects on sleep and the circadian rhythm [84]. The fourth type of melatonin receptor is RZR/RORα (retinoid-related orphan nuclear hormone receptor), located in both the periphery and the brain as a nuclear receptor [77, 85] and responsible for immunomodulation at the periphery, cellular growth, and bone differentiation [85].

Melatonin in Allergic Disease, Atopy, and Related Sleep Disorders

As melatonin improves sleep and strengthens and aligns circadian rhythms, it may have some effects on allergic disease. Melatonin's antioxidative and immunological effects have been documented in *in vivo* and *in vitro* studies [21, 86–89]. Various types of immune and skin cells produce melatonin and express melatonin receptors

[45, 90, 91]. Melatonin stimulates important antioxidative enzymes relevant to allergic/atopic diseases, like superoxide dismutase, glutathione peroxidase, and glutathione reductase, which protect membranes from oxidation and toxic radicals [82, 83].

Melatonin also has various modulatory effects on the immune system in allergic diseases [21, 92, 93]. Th1 and Th2 cells express membrane and nuclear receptors for melatonin; via these receptors, melatonin induces synthesis of IFN-ɣ, IL-2, IL-6, and IL-12 by lymphocytic and monocytic cell lines and amplifies melatonin receptors in lymphocytes [21, 45, 94, 95]. Melatonin also influences the activity of proinflammatory cells: NK cells, T and B lymphocytes, granulocytes, monocytes, and mast cells [21, 45, 96]. Some studies show melatonin has immunomodulation functions, while others show it has anti-inflammatory abilities. As a result, melatonin has been suggested to act as an immune buffer by acting as a stimulant under baseline or immunosuppressive conditions and producing anti-inflammatory effects in states of acute inflammation [21, 97]. Whether and how these pathways act in human allergic diseases have not been extensively explored. Most of the available data are from studies on two diseases – allergic dermatitis and asthma.

Allergic dermatitis, or eczema, is a common skin condition often starting in early childhood [21, 98]. Its pathogenesis is complex and only partially known. The clinical manifestations include eczema, erythema, edema, excoriation, scaling, and itching. Acute lesions of allergic dermatitis are caused by Th2-dependent cytokines, specifically IL-4 (involved in IgE switching and allergy development), IL-5 (attaching eosinophils), and IL-13 (a mediator of allergic inflammation). Chronically, there is a switch to cytokines derived from Th1 cells, leading to interferon-gamma (IFN-ɣ) release. Generally, IFN-ɣ increases melatonin synthesis [97], although the mechanisms are unclear. For the subset of allergic dermatitis patients with poor sleep, however, there is a tendency toward lower levels of IFN-ɣ [99], which may result in lower melatonin levels [100], resulting in poor sleep and poor control of the allergic disease.

Melatonin may have a bidirectional relationship with inflammatory cytokines in allergic dermatitis, and supplementing with melatonin, given its antioxidant and anti-apoptotic effects, may help protect skin integrity and maintain the epidermal barrier. In animal studies, melatonin suppressed the development of the atopic dermatitis-like condition in mice by reducing total serum IgE, IL-4, and IFN-ɣ produced by CD4+ T cells [101]. In a subset of children with atopic dermatitis, higher levels of endogenous melatonin were associated with better sleep [99, 102]. In the same study, those with reduced nocturnal melatonin had more sleep disturbance and greater severity of allergic disease [99]. Furthermore, a randomized clinical trial showed that melatonin supplements were safe and effective among 48 children with allergic dermatitis and led to improvements in allergic dermatitis and sleep [45].

Given the above evidence, melatonin has potential as an antioxidant, anti-inflammatory, and immunomodulatory agent in allergic dermatitis. However, little data on the use of melatonin in this condition are available. The abovementioned clinical trial, which employed a randomized double-blind placebo-controlled crossover design, included 73 children aged 1–18 years with atopic dermatitis and showed that melatonin (3 mg/day) for 4 weeks decreased the severity of atopic dermatitis, shortened sleep-onset latency by 21.4 min, and did not cause adverse

events [45, 103]. However, it did not decrease pruritus. Further studies are needed to confirm these findings and determine appropriate dose and long-term therapeutic potential and mechanisms of improvement.

Asthma, another common allergic disease, is characterized by chronic airway inflammation, airway hyper-responsiveness, and expiratory airflow limitation. Asthma is associated with elevated levels of oxidants, including endogenous inflammatory cells and exogenous smoke and toxic gases [104–106]. Patients with nocturnal asthma have shown circadian variation in airway inflammation, with nighttime worsening linked to elevated airway inflammation, airway hyper-responsiveness, and worsened airflow limitations [107].

Despite melatonin's known antioxidant properties, the data are unclear about melatonin's role in asthma, and melatonin can in fact have paradoxically harmful effects. These negative effects are related to melatonin's pro-inflammatory role in asthma. Melatonin increases pro-inflammatory cytokines in vitro (IL-1, IL-6, and TNF-α) by peripheral blood mononuclear cells and alters inflammatory characteristics of the cells [108, 109]. An experimental model of allergic airway inflammation showed replacing melatonin after pinealectomy restored airway inflammation [110]. Melatonin also promoted expression of chemotaxins in lung epithelial cells [111]. Additionally, melatonin receptors have been isolated in lung tissue [112], and melatonin increases airway smooth muscle tone [113], which may worsen asthma. Levels of melatonin are higher in patients with nocturnal asthma than those with non-nocturnal asthma and healthy controls, suggesting nocturnal asthma exacerbations may be related to changes in melatonin levels [114]. These synergistic effects toward inflammation and airway narrowing suggest that inhibiting melatonin may paradoxically benefit patients with asthma [111].

On the other hand, some studies reported melatonin's favorable action in bronchial asthma. In contrast to the previously mentioned findings that melatonin is higher in asthmatics, another study found melatonin was lower in asthmatics than controls [115], suggesting that melatonin, with its theoretical effects to combat oxidation and inflammation, may be involved in the pathophysiology of asthma. These differing levels of melatonin in asthmatics may be due to different responses to melatonin in patients with asthma based on subtype – nocturnal versus non-nocturnal asthma. Ultimately data regarding melatonin in asthma patients remain indeterminate.

Besides being a potent free radical scavenger, melatonin also regulates gene transcription in mucus production [116]. In an in vitro model for asthma using human epithelial cells, melatonin significantly inhibited mucus production via suppressing expression of mRNA and protein levels of MUC5AC, a major component of mucin. Nuclear factor-κB is an important transcription factor in asthma that leads to increased expression of other genes responsible for pro-inflammatory cytokines, chemokines, and adhesion molecules [117]. Melatonin partially inhibits expression of nuclear factor-κB in a rat model of asthma [118]. Furthermore, some asthmatics have mostly neutrophilic airway inflammation, which is correlated with a worse outcome and lower response to inhaled steroids [119]; melatonin inhibits neutrophil rolling and infiltration and, due to its antioxidant properties, could counteract superoxide production by neutrophils [120].

Based on the current evidence indicating negative effects of melatonin in experimental models of asthma and higher melatonin levels in patients with nocturnal asthma, the use of exogenous melatonin as a sleep promoting agent is not recommended in asthma patients [108, 111]. Although positive effects have been reported [115] with melatonin in asthma, it is concerning that in other studies melatonin has effects ranging from no effect to harmful for asthma. Specifically, in a randomized, double-blind, placebo-controlled study, melatonin 3 mg given nightly for 4 weeks improved subjective sleep quality in asthmatics ($n = 12$) compared to placebo ($n = 10$), with no significant difference in asthma symptoms, the use of relief medication, or daily peak expiratory flow rate [121]. However, in another study done on asthma patients and normal controls, melatonin was pro-inflammatory in both groups, causing significantly increased production of inflammatory cytokines (IL-1, IL-6, TNF-α) between 16:00 and 04:00 from 24-h sampling of peripheral blood mononuclear cells [108]. Melatonin given in concentrations between 10^{-12} and 10^{-5} M — which includes the physiologic melatonin range between 10^{-9} and 10^{-7} M — was pro-inflammatory to peripheral blood mononuclear cells collected from asthma patients and healthy subjects, particularly in the presence of TNF-α [111]. These results suggest possible adverse effects of exogenous melatonin in asthma and that more data are needed for melatonin use in allergic diseases and associated sleep problems.

Sleep-disordered breathing is typified by abnormalities in respirations in sleep and categorized into obstructive sleep apnea, central sleep apnea, sleep-related hypoventilation, and sleep-related hypoxemia [112]. Melatonin has positive effects on complications caused by sleep-disordered breathing, such as preventing hyperglycemia that follows exposure to intermittent hypoxia [113], inhibiting expression of inflammatory cytokines (TNF-α and IL-6) [114], mitigating abnormal cardiovascular physiology [115], and ameliorating subsequent secondary hypertension [116]. The inflammatory cascade triggered by sleep-disordered breathing is of importance for atopic/allergic disease. In patients with obstructive sleep apnea, prophylactic melatonin protects against chronic intermittent hypoxia-induced myocardial inflammation and fibrosis via actions on the MT1 and MT2 receptors [117]. However, role of melatonin in sleep-disordered breathing related to allergic disease, especially in asthma, is uncertain given the potential effect as pro-inflammatory agent and the limited studies to date.

Melatonin Supplements for Sleep

Exogenous melatonin supplements decrease sleep latency even in small doses such as 0.1–0.3 mg per day [122]. Immediate-release formulations cause blood levels of melatonin to peak around 20–60 min and have short circulatory half-lives of around 40–60 min [123]. Melatonin supplementation has a significant but rather modest effect at promoting sleep; in a meta-analysis of information from 17 different studies involving a total of 284 subjects, melatonin (dosed between 0.1 and 50 mg) reduced sleep-onset latency by 4 min, increased sleep efficiency by 2.2%, and increased total sleep duration by 12.8 min [123]. Melatonin is useful in resetting the

body's sleep-wake cycle and reducing the time it takes to fall asleep in situations related to jet lag, shift work, and delayed sleep-wake phase disorders [124–126].

Exogenous melatonin has a more robust effect in altering the circadian rhythm in humans in accordance to a phase-response curve that is nearly opposite of what is seen for light exposure [127]. Melatonin given in the late afternoon or evening advances the sleep time, also known as a phase-advance effect. Melatonin administration from the early morning to noon has a phase-delay effect [128]. Melatonin's effects of acute sleep promotion and its ability to alter circadian rhythms after repeated dosing are complementary.

Side effects reported with melatonin supplements are headaches, daytime sleepiness, dizziness, nausea, gastrointestinal upset, confusion, sleepwalking, vivid dreams, or nightmares [129–131]. With long-term use, there have been some reports of tolerance on melatonin supplements [129], which may be related to melatonin-induced internalization of melatonin receptors [132, 133]. With loss of efficacy of the melatonin supplement, there can be recurrence of sleep symptoms.

Melatonin controlled-release tablets received approval from the European Medicines Agency for insomnia treatment in patients over 55 years of age in Europe [76]. The usual dose is 2 mg/day [134]. In a study on patients with amyotrophic lateral sclerosis, doses as high as 300 mg/day for up to 2 years were shown to be safe [85]. In comparison to regular melatonin, which has a very short half-life of 20–30 min on average with a maximum of 45 min [33], controlled-release tablets have an initial faster release of about a third of the dose in the first hour followed by a slower prolonged release for up to 8 h [135].

Melatonergic Pharmaceuticals in Sleep Medicine

Melatonin agonists are synthetic melatonergic drugs that can provide the acute sleep promotion effect. Ramelteon is a nonselective MT1/MT2 melatonin receptor agonist that received US FDA approval in 2005 for treatment of insomnia in individuals with difficulty falling asleep [136]. It has 84% gastrointestinal absorption and a circulatory half-life of 1–2 h [137] and is mainly metabolized by CYP1A2, CYP2C9, and CYP3A4 [138]. Among melatonergic agonist drugs, ramelteon has relatively high affinity to both MT1 and MT2 receptors [76].

Tasimelteon is another MT1/MT2 receptor agonist. It was approved by the FDA in 2014 for the treatment of non-24-h sleep-wake disorder. In 2015, it was approved in Europe for the treatment of non-24-h sleep-wake disorder in blind adults. It has a half-life of 2 h and is metabolized by CYP1A1, CYP1A2, CYP2D6, and CYP2C9 [139]. Its sleep-initiating and antidepressant effects are being examined [76].

Agomelatine is a nonselective melatonin receptor (MT1/MT2) agonist and 5-HT2c antagonist that received approval from the European Medicines Agency in Europe for treatment of major depression in adults [76, 80, 140]. However, it was dropped by pharmaceutical companies for development in the USA after some cases of elevated hepatic transaminases were reported during treatment of depression. It is mainly metabolized by CYP1A1, CYP1A2, and CYP2C9 [138].

TIK-301 is a melatonin receptor agonist and serotonin receptor antagonist drug with more powerful antagonism of 5-HT2c and 5-HT2b receptors when compared to agomelatine [141]. It has a half-life of 1 h [142]. The FDA approved its use for sleep disorders of blind people with no light perception and non-24-h circadian rhythm [76].

The melatonin antagonist pharmaceuticals – luzindole (competitive for MT2-R), P-PDOT (selective for MT2-R) [78], and S29434 (potent for MT3-R) – are compounds used in research of melatonin receptors [77, 84]. These molecules are useful in elucidating localization and functional roles of the specific receptors in native systems. For example, activation of the MT2 receptor enhances splenocyte proliferation and inhibits leukocyte rolling in the microvasculature, whereas activation of the MT3 receptor reduces intraocular pressure and inhibits leukotriene B4-induced leukocyte adhesion [78]. These immunological cascades have been implicated in chronic inflammatory skin diseases and may be helpful in investigations of melatonin's role for allergic/atopic diseases. For more information on sleep medications, see the pharmaceuticals chapter.

Regulation of Melatonin in the Marketplace and Potential Consequences

Due to melatonin's status as a dietary supplement in the USA, it has achieved widespread use. In the USA, melatonin is the fourth most popular supplement for adults and the second most popular supplement for children [4, 5]. It is marketed as a medicine in most countries in the world, including Europe and Asia Pacific, where it is available by prescription only. Melatonin's application as a dietary supplement accounts for the largest portion of its global demand and is projected as the largest growth segment [6].

In the USA, immediate-release melatonin is available as an over-the-counter at dosages ranging between 0.5 and 10 mg. Previously, melatonin was derived from animal pineal tissue (e.g., cow), and now formulations come from synthetic or plant sources and do not carry a risk of contamination or the means of transmitting infectious material [143]. In the setting of endogenous level of melatonin being in the picogram to microgram range, oral doses in the range of 0.3–1 mg result in physiologic concentrations of melatonin in the serum [144]. However, North American pharmacy aisles have doses marketed as ten times those amounts.

In studies, melatonin at very large doses (as high as 100 mg/day) in healthy adults were well tolerated with only reported side effect being mild drowsiness [145]. Although there is no evidence to date that too much melatonin is fatal or life-threatening, an excess can upset bodily processes and rhythms, producing symptoms including drowsiness, hypothermia, overproduction of prolactin, and disruption of menstrual cycles, puberty, and normal hormonal development in young individuals [124, 144, 146].

Long-term effects of melatonin on prepubertal children are not completely known [147]; however, melatonin is also known as anti-gonadal hormone based on available data [148, 149]. The longest studies of long-term melatonin use in children had follow-up of 3.7 years (mean) in children with ADHD and sleep-onset insomnia [150], up to 18 months in children with chronic insomnia [151], and up to

6 years in blind, mentally retarded children with severely disturbed sleep for maintaining circadian rhythm [152]. In all three studies, the side effects were determined by subjective report. In this last study in blind children, melatonin was given at doses between 0.5 and 4 mg; only one patient started therapy before puberty, and he developed a eunuchoid body habitus, with puberty not yet begun at 14 years old. This patient's gonadotropin hormones were at normal prepubertal levels, and growth rate and skeletal development were normal, but no growth spurt had occurred [152]. Although human data are limited, melatonin's effect on prepubertal animals may be related to systems other than the pineal gland, as its anti-gonadal effects occurred in pinealectomized versus intact animals [153]. Further animal studies suggest that anti-gonadal action of melatonin in the brain involves suppression of the release of gonadotropin-releasing hormone [154, 155].

In terms of how much supplementation can have an effect, doses of melatonin as little as 1 μg (20 μg/kg) reduced gonad size and fertility in rodents. Melatonin implants in cats inhibited estrus and advanced puberty onset in primates by 5 months [147]. Doses well below those for children had physiological effects on gonad function in rodents and primates. For children, 3 mg oral tablet of melatonin equals 200 μg/kg for a child weighing 15 kg (33 lb) or 60 μg/kg for a child weighing 50 kg (110 lb). Thus, melatonin's potential adverse effects in human children should be considered against potential benefit for treating sleep issues related to allergic diseases.

Another concern is that the actual dosage of melatonin supplements can vary greatly from label claims. Quantified melatonin in commercial supplements across various brands and forms ranged between −83% and +478% of the labelled content and had lot-to-lot variability of up to 465%. Serotonin (5-hydroxytryptamine), a related indoleamine and a target of medications used in treatment of several neurological disorders, was identified in over a quarter of the supplements at physiologic levels [156]. A liquid formulation of melatonin, though suspected to be the least stable due to melatonin's known instability at room temperature in solvent, was generally reliable to the label claim, with low lot-to-lot variability. The most variable formulation was a chewable tablet, which is unfortunately also most likely to be used by children. The lowest melatonin content compared to its label claim value was in a capsule, which also contained other herbal extracts. The chewable tablet and capsule also showed the greatest variability between lots [156]. After storage containers are opened, melatonin degradation occurs strongly within 2 days without airtight conditions when kept at room temperature in light or darkness [157]. These quality control issues can result in inaccurate dosing of melatonin in treating sleep disorders. Dosages that are too low may be ineffective, and higher doses can result in unpleasant or unexpected side effects. Furthermore, night-to-night variability in dose may be interpreted as failure of efficacy.

Conclusions and Future Directions

Melatonin's secretion by the pineal gland in a circadian rhythm helps to regulate sleep phase. Melatonin also has a small but significant effect on sleep onset, duration, and efficiency [123]. In addition, the antioxidant and immunomodulatory

effect of melatonin suggest that it is a candidate for treating sleep issues comorbid with allergic diseases, particularly allergic dermatitis. But given data on a pro-inflammatory effect on asthma, more clinical data are needed, especially those using objective assessments of sleep quality via actigraphy and polysomnography, allergy testing, and melatonin levels. In asthma, melatonin as a sleep-inducing agent has been safely used, but its routine use is not recommended in bronchial asthma due to the potential pro-inflammatory effects and bronchial constriction. Future studies would also benefit from larger sample sizes and representation of specific age and racial groups at high risk for poor sleep quality and related illnesses [158, 159]. Given that allergic diseases and sleep issues can start in early childhood and that melatonin is a neuroendocrine molecule, longer-term follow-up studies of the effect of melatonin on children's developing endocrine systems are important. Additionally, further evaluation of melatonin administration in allergic/atopic diseases such as allergic dermatitis and asthma could elucidate the role of melatonin in clinical applications.

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Pharmacologic Management of Allergic Disease and Sleep

28

Natalia M. Jasiak-Panek, Kevin T. Le, Thomas Moran, and Sukhraj Mudahar

Allergic disease in children encompasses various medical diagnoses including but not limited to asthma, allergic rhinitis (AR), and atopic dermatitis (AD). Asthma is the most prevalent pediatric chronic disease, AR affects up to 40% of children, and AD affects up to 30% of children [1, 2]. Up to 60% of children with allergic diseases develop sleep disturbance (SD) [2, 3]. The spectrum of SD includes difficulty falling asleep, frequent nighttime awakenings, and difficultly waking in the morning. Although the exact pathophysiology of SD is unknown, several mechanisms have been proposed. One possible mechanism is reduced nocturnal melatonin secretion. Melatonin, a hormone made primarily by the pineal gland in the brain, regulates sleep and wake cycles but also has immunomodulatory, anti-inflammatory, and antioxidative effects.

Pruritus and scratching movements also contribute to sleep disturbance. Studies have shown that a higher pruritus score is associated with more nighttime movements and lower sleep efficiency [3, 4]. Itching may worsen at night due to the circadian rhythm of T-cell-mediated inflammation and increased skin sensitivity to allergens at night [3]. Studies suggest that inflammatory cytokines undergo circadian fluctuations and contribute to greater symptomatology at night for patients [5]. Other proposed mechanisms include higher IgE levels leading to lower sleep efficiency and higher levels of serotonin and interleukin-31 inducing pruritus. Furthermore, studies have shown that poor asthma control results in a higher degree of SD in children [6].

N. M. Jasiak-Panek (✉) · K. T. Le · T. Moran · S. Mudahar
Department of Pharmacy, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: njasiak@luriechildrens.org

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Patients with allergic diseases can have poor illness response if they do not get adequate sleep, and therefore it is especially important to treat insomnia in this population. Sleep deprivation can impair physical and mental health, alter immune response, and even delay wound healing [1]. If left untreated, SD may have detrimental consequences on children including impaired neurocognitive and motor function, behavioral problems, mood changes, decreased growth, and poor quality of life [2, 3, 5]. The management of SD is a challenge in this population given the limited availability of well-designed studies, but most clinicians and guidelines agree that improving sleep is a key aspect of disease control [3].

The following chapter reviews the available pharmacological therapies for the treatment of SD in pediatric patients with allergic diseases. The chapter will review antihistamines (oral and nasal), melatonin, clonidine, chloral hydrate, doxepin, montelukast, benzodiazepines, hypnotics (zaleplon, zolpidem, and eszopiclone), topical therapies, steroids (topical, inhaled, and intranasal), and immunomodulatory therapies (calcineurin inhibitors, antimetabolites, steroids, and dupilumab). Lastly, a review of pregnancy and lactation considerations is also included.

Antihistamines

Oral Antihistamines

Systemic antihistamines block histamine release from mast cells and basophils, which in turn prevents the stimulation of local blood vessels and nerves to produce vasodilation and pruritus [7]. First-generation H_1 histamine receptor antagonists (H_1RAs) such as diphenhydramine or hydroxyzine are often used as sleep aids in allergic conditions [5, 8, 9]. Their highly lipophilic properties allow them to cross the blood-brain barrier (BBB) and saturate approximately 75% of the H_1 receptors in the brain resulting in sedation. Histamine is important in regulating the sleep-wake cycle, cognition, and memory, and therefore blockage of the H_1 receptor leads to impairment of central nervous system (CNS) function. Given the risks associated with CNS depression, it is recommended that first-generation H_1RAs are restricted to children with urticarial or atopic dermatitis whose pruritus is so severe that sedation with an H_1RA outweighs the risks [10]. In addition to CNS depression, first-generation H_1RAs also cause a number of anticholinergic side effects such as blurred vision, urinary retention, constipation, and xerostomia.

In a double-blind, placebo-controlled clinical trial, the efficacy of diphenhydramine 1 mg/kg for sleep was studied in a population of 50 pediatric patients [11]. Using sleep records, researchers assessed sleep latency (difficulty falling asleep for 45 min or more), number of awakenings, and duration of sleep. Also, a global assessment of sleep disturbance severity and the efficacy of the diphenhydramine versus placebo were analyzed each week. The results of the study showed that diphenhydramine was significantly better than placebo in reducing sleep latency time and number of awakenings. However, duration of sleep only marginally increased with diphenhydramine. The conclusion of the study was that diphenhydramine was an

effective and safe agent for sleep disturbance in pediatric patients. If diphenhydramine is given immediately before bedtime, then it can reduce sleep latency time and number of awakenings [12]. Typical diphenhydramine duration of action is approximately 4–6 h. However, daytime sedation has been reported even if given immediately prior to bedtime. Histamine antagonism also results in anti-inflammatory effects preventing histamine release from mast cells and basophils leading to reduced itching. Despite initial efficacy for reducing sleep disturbance, the risk of tolerance may develop to the sedative properties as early as 4 days after therapy initiation and consecutive daily use. In fact, a study looking at routine use of antihistamine to treat any sleep disorder was discontinued prematurely due to lack of efficacy and risk of side effects in infants [13].

In a multicenter, double-blind study of 155 children treated with chlorpheniramine (1 mg/day for children aged 1–5 years and 2 mg/day for children aged 6–12 years) versus placebo for AD symptoms over a 4-week duration, chlorpheniramine did not alleviate itching more than placebo [14]. On the contrary, pruritus was significantly suppressed for up to 24 h after a single oral dose of hydroxyzine 0.7 mg/kg in 12 children (mean age 6.1 ± 4.6 years) [15]. In a subsequent study, hydroxyzine 0.7 mg/kg three times daily versus 1.4 mg/kg three times daily showed similar efficacy, but increased sedation was reported in the higher-dose group [15]. One double-blind randomized controlled trial compared the efficacy of hydroxyzine versus cyproheptadine for pruritus relief in children between the ages of 2–16 years [16]. Hydroxyzine showed improvement in both day and nighttime pruritus to a greater extent than cyproheptadine. Sedation was the major adverse effect reported in both groups.

Second-generation antihistamines such as cetirizine and loratadine are less sedating antihistamines, and third-generation antihistamines such as desloratadine, fexofenadine, and levocetirizine are non-sedating metabolites of second-generation agents (Table 28.1) [17, 18]. Both second- and third-generation antihistamines have preferential binding to peripheral H_1 receptors when compared to first-generation antihistamines, resulting in minimal penetration across the BBB and limited activity on serotonergic, cholinergic, and alpha-adrenergic receptors. Furthermore, although some second-generation antihistamines are lipophilic such as loratadine, they still cannot pass through the BBB. Research suggests that second- and third-generation antihistamines cannot penetrate the BBB as they are substrates of P-glycoprotein (P-gp) [19]. P-gp is a drug transport protein that pumps drugs out of cells. In the brain it plays a detoxifying role by preventing P-gp substrates, such as non-sedating antihistamines, from crossing the BBB.

The efficacy of cetirizine in mild to moderate AD was studied in children aged 6–12 years in a double-blind placebo-controlled trial. Patients received either 5 mg/kg/day if 30 kg or less or 10 mg/kg/day if greater than 30 kg [20]. Compared to placebo, cetirizine-treated patients experienced improvement in all signs and symptoms of AD (73% cetirizine versus 18% placebo; $P < 0.02$). However, according to a review of 16 studies, no evidence exists to support the effectiveness of second-generation antihistamines in treating atopic dermatitis [21]. Following this meta-analysis, a study by Ng and colleagues showed that cetirizine has sedative properties in children when compared to chlorpheniramine [22]. Diepgen et al. also found that

Table 28.1 Dosing, dosage forms, and sedative properties of select antihistamines

Drug	Dosing indication	Pediatric oral dosing	Sedative properties	IV/IM	Oral tablet or capsule	Oral liquid
First-generation antihistamines						
Diphenhydramine	Insomnia	2–12 years, 1 mg/kg/day (maximum: 50 mg); children >12 years and adolescents, 50 mg/day	Strong	X (IV)	X	X
Hydroxyzine[a]	Sedation, pruritus	Sedation, 0.6 mg/kg/day (maximum 100 mg); pruritus, children <6 years, 37.5–50 mg/day in divided doses; children >6 years 50–100 mg/day in divided doses	Strong	X (IM)	X	X
Second-generation antihistamines						
Cetirizine[c]	Urticaria or allergic rhinitis	Children 2 to 5 years: Initial: 2.5 mg once daily; dosage may be increased to 2.5 mg twice daily or 5 mg once daily; maximum daily dose: 5 mg/day Children ≥6 years and Adolescents: 5 to 10 mg once daily	Mild		X	X
Loratadine[c]	Urticaria, allergic rhinitis	Urticaria, 2–12 years, 5 mg/day; adolescents, 10 mg/day; rhinitis, children 2 to <6 years, oral liquid or chewable tablet, 5 mg/day; children >6 years and adolescents, oral liquid, capsule, tablet or chewable tablet, 10 mg once daily; dispersible tablet, 5 mg twice daily or 10 mg once daily	Mild		X	X
Third-generation antihistamines						
Desloratadine[c]	Urticaria and allergic rhinitis	6–11 months, 1 mg once daily; 12 months to 5 years, 1.25 mg once daily; 6–11 years, 2.5 mg once daily; children >12 and adolescents, 5 mg daily	Non-sedating		X[b]	X
Fexofenadine[c]	Respiratory allergies and urticaria	Children 2 to 11 years: Oral suspension or orally disintegrating tablet (ODT): 30 mg twice daily Children ≥12 years and Adolescents: Orally disintegrating tablet (ODT): 60 mg twice daily Extended release tablet: 180 mg once daily	Non-sedating		X[b]	X
Levocetirizine[c]	Urticaria	6 months to 5 years, 1.25 mg once daily; 6–11 years, 2.5 mg once daily; children ≥12 years and adolescents, 5 mg daily	Non-sedating		X	X

[a]May require dose adjustment in hepatic impairment.
[b]Fexofenadine and desloratadine also available as orally disintegrating tablet.
[c]May require dose adjustment in renal dysfunction.

cetirizine reduced the duration and amount of topical corticosteroids used in both infants and children when compared to placebo [23].

Due to reduced side effect profile when compared to first-generation H_1RAs, second- and third-generation H_1RAs are typically preferred for treatment of all other symptoms related to allergic disease with the exception of insomnia. Given that second-generation H_1RAs lack sedative properties, their use for SD is not supported by the available literature. Furthermore, histamine is one of many pruritus-inducing mediators, and therefore antihistamines do not always lead to full symptom relief [18].

The safety of antihistamines in children has been put into question by many drug agencies worldwide including the Federal Drug Administration (FDA) as many antihistamine indications in children have been extrapolated from adult data [24]. Furthermore, there is minimal antihistamine pharmacokinetic data on pediatric dosing for different pediatric age groups. Over 1500 children under the age of 2 were treated in US emergency departments from adverse events after receiving a cough and cold medication that contained either an antihistamine or decongestant between 2004 and 2005 [25]. Due to possible life-threatening side effects, the FDA recently issued a statement that children under the age of 2 should not be given any cough and cold products that contain a decongestant or antihistamine.

According to the National Institute for Health and Care Excellence (NICE) clinical guidelines from the United Kingdom, sedating antihistamines are indicated for a short duration (7–14 days) in children with SD [26]. If children respond to therapy after initial trial, then short courses of first-generation antihistamines may be repeated. In children who suffer from severe itching or urticaria without SD, then non-sedating antihistamines are preferred over sedating antihistamines. Non-sedating antihistamines may be continued for 1–3 months, but patients should be evaluated at least every 3 months, and long-term use of these therapies is not recommended.

Intranasal Antihistamine

According to the allergic rhinitis clinical practice guidelines, intranasal antihistamines are an option for patients with seasonal (caused by IgE-mediated response to seasonal allergens), perennial (caused by IgE-mediated response to year-round environmental allergens), or episodic AR (caused by IgE-mediated response to an exposure that is not routinely present in household) [27]. Intranasal antihistamines are indicated in patients 6 years or older who have failed an adequate trial of a nasal steroid or oral antihistamine. Compared to intranasal steroids and oral antihistamines, intranasal antihistamines have a more rapid onset of action (15–30 min). Common concerns with this class of medications include increased cost relative to oral antihistamines, bitter taste, more frequent dosing, epistaxis, and nasal burning. Currently azelastine and olopatadine (both second-generation H_1RAs) are the only two intranasal antihistamines with FDA approval in the United States and are available by prescription only. Both azelastine and olopatadine may be administered as one spray twice daily in children between the ages of 6–11 years and increased to two sprays twice daily in children 12 years or older. Olopatadine is available as a

0.6% nasal spray. Azelastine is available as a 0.1% and 0.15% spray as well as a combination product with fluticasone. For the treatment of nasal symptoms, intranasal antihistamines are non-inferior and even superior in some studies than oral antihistamines. In patients who fail oral antihistamines, intranasal antihistamines may provide some symptom relief in AR. However, due to localized effects and the reduced likelihood of somnolence with second-generation antihistamines, treatment of SD is not effective with intranasal antihistamines. In patients who require an intranasal antihistamine and cannot tolerate the bitter taste, azelastine 0.15% plus sorbitol and sucralose has improved taste compared to other formulations.

Melatonin

Melatonin is an endogenous hormone that is essential for sleep due to its regulatory effects on the circadian rhythm [2, 4, 5]. Although secreted primarily by the pineal gland, melatonin is also partially secreted by skin cells and lymphocytes, both of which also express melatonin receptors [2]. While utilized primarily for its sedative effects, melatonin also has a modulatory effect on sleep disturbances caused by AD due to its immunomodulatory, anti-inflammatory, and anti-oxidative ability, which can improve symptomatic manifestations of atopic dermatitis such as inflammation and itching as well as decrease inflammatory markers that may be associated with sleep disturbances [2, 4].

Chang et al. studied the effects of exogenous melatonin on 38 children and adolescents aged 1–18 years with AD involving at least 5% total body surface area [4]. Patients were randomized to receive either 3 mg/day of melatonin or placebo for 2 weeks at which point they would receive the alternate treatment for another 2 weeks. The primary outcome for the study was the severity of disease as determined by the Scoring Atopic Dermatitis (SCORAD) index. The researchers found a statistically significant reduction SCORAD scores by 9.1 for treatment with melatonin compared to placebo. In addition, sleep latency was reduced by 21.4 min with melatonin treatment. However, there was no correlation between improvement in SCORAD scores and sleep latency. This study confirmed an older study by the same researchers in which they found low melatonin secretion in patients with AD was associated with decreased sleep efficiency, but those patients which had a higher compensatory increase in melatonin due to the sleep disturbances had better sleep efficiency, less sleep fragmentation, and milder disease severity [28].

Melatonin exerts its sedative properties via agonist activity at MT1 and MT2 melatonin receptors in the suprachiasmatic nucleus, the region of the hypothalamus associated with regulation of circadian rhythms, resulting in a phase shift in the rhythm [29]. Specifically, activity at the MT1 receptor can increase the amplitude of the circadian clock oscillations, and activity at the MT2 receptor can help synchronize the circadian clock [30]. Based on available evidence, melatonin "induces the synthesis of interferon-γ, IL-2, IL-6, and IL-12 by lymphocytic and monocytic cell lines along with influencing the activity of natural killer cells, T and B lymphocytes, granulocytes, monocytes, and mast cells" [4]. Additionally, melatonin has shown to

have anti-inflammatory properties in periods of acute inflammation and acts conversely in basal conditions [31]. Data suggests that treatment with melatonin reduces the activation of mast cells in the skin, which could further alleviate symptomology associated with AD [2, 32, 33]. Neutralization of free radicals and stabilization of cell membranes may help repair damaged skin and improve wound healing [2, 4].

There is significant variability associated with the potency of over-the-counter melatonin products. One recent study analyzed 31 different melatonin supplements and found that actual content can range from −84% to +478% of the labeled content [34]. Significant variability also existed from lot to lot of the same product and capsules tended to have the highest increase in actual content versus labeled content. Researchers noted that tablets or sublingual tablets with the simplest ingredients, such as melatonin added to cellulose to silica, tended to have the least variability.

The drug is generally well tolerated and has a low incidence or absence of adverse effects. Headaches, dizziness, nausea, and drowsiness have been reported with melatonin use, but the incidence is not significantly different when compared to placebo [35]. Because melatonin can stimulate the immune system, it should be avoided in patients with autoimmune disorders [5]. The one randomized control trial conducted in pediatric patients (aged 1–18 years) with atopic dermatitis utilized 3 mg/day of melatonin given orally at bedtime, but the daily dose can vary from 0.75 to 6 mg [4, 36].

While melatonin receptor agonists (ramelteon, tasimelteon) may play a role in the modulation of disease severity and sleep quality in patients with allergic diseases, these agents have not specifically been studied in this patient population.

Clonidine

Clonidine is an alpha-2 agonist utilized primarily for hypertension but which can also be effective in the treatment of pain and withdrawal [37]. Studies have shown that clonidine is effective in the treatment of attention-deficit/hyperactivity disorder (ADHD) and is a sedative with dose-dependent effects on sleep architecture [38–41]. In addition, clonidine has been shown to reduce pruritus, which can be beneficial in aiding sleep quality in patients with AD [37].

Clonidine acts on both peripheral and central alpha-2 adrenergic receptors. Agonist activity at central presynaptic alpha-2 receptors leads to a negative feedback inhibition and a decrease in sympathetic activity and increased vagal tone [42]. The resultant reduction in the release of norepinephrine can result in a sedative effect most often observed as a side effect of its use as a antihypertensive agent, decrease in the duration of REM sleep, and decreased sleep latency [5, 42, 43].

Animal studies by Gotoh et al. have shown that intrathecal clonidine inhibits the itch reflex associated with the injection of a pruritogenic agent in mice [44, 45]. The effect was antagonized by the injection of yohimbine, a nonselective alpha-2 antagonist and not by prazosin, which selectively antagonizes alpha-2b and alpha-2c [44]. Therefore, the authors hypothesized that the primary mechanism of action of clonidine in the treatment of pruritus is mediated via the alpha-2a receptor in the

dorsal horn of the spinal cord, potentially through the inhibition of gastrin-releasing peptide [37, 44]. Since these animal studies, there have been case reports describing success with the use of clonidine for intractable itching associated with atopic dermatitis and herpes zoster [37, 46].

Clonidine is generally well tolerated, and the most common side effects include dose-dependent dry mouth, drowsiness, dizziness, constipation, bradycardia, and sedation [42]. The drug should be slowly tapered off because abrupt discontinuation can lead to a rebound hypertension and the American Academy of Child and Adolescent Psychiatry recommends a cardiovascular evaluation prior to initiation of clonidine and periodically throughout treatment [42].

While the drug can be given via numerous routes of administration, including intravenous, oral, transdermal, or epidural, it is typically given via the oral route for sleep [42]. Due to quick onset and short half-life of the immediate release formulation, there may be incidents of mid-sleep awakenings and rebound hyperarousal which may lead to nightmares or night terrors, which may be alleviated with the use of the extended-release formulation [42, 47]. Patients that have diabetes or Raynaud's syndrome should avoid clonidine [48].

While no specific dosing recommendations exist for insomnia associated with allergic diseases, the drug has been utilized for patients with ADHD at starting doses of 0.05 mg for patients 4–17 years of age which can be titrated in 0.05 mg increments to a max dose of 0.4 mg per day, while younger and/or underweight patients may require this dose to be cut in half [42, 49].

Chloral Hydrate

Chloral hydrate is a sedative/hypnotic agent that has been routinely used for sedation since the 1800s [50]. Though the exact mechanism of action is unknown, it is potentially related mechanistically to benzodiazepines due to the effect of its active metabolite, trichloroethanol, on the GABA receptor [5].

Currently not available in the United States as an FDA-approved drug product, it was discontinued in 2012 due to business reasons [51]. Numerous errors have been reported over the years with the FDA-approved product, many which led to fatal events in patients due to supratherapeutic dosing, inadvertent administration through the wrong route, and adverse effects associated with chloral hydrate use such as cardiac toxicity and respiratory depression [50, 51]. While the FDA-approved product has been withdrawn from the market, chloral hydrate powder is still available for compounding by pharmacies for individual prescriptions [51]. However, recent literature suggests that the compounded product has a shorter duration of action than the FDA-approved formulation and can lead to sedation failures and need for additional sedative agents [51, 52]. In addition, the reformulated product requires twice the amount of volume per dose as the FDA-approved product, which combined with its propensity to irritate the GI tract and bitter taste, can lead to vomiting.

The long half-life of its active ingredient, trichloroethanol, can lead to delayed sedation after discharge, and its narrow therapeutic index leaves little room for dosing errors [50, 51]. Most significantly, chloral hydrate use is directly related to respiratory depression and respiratory arrest [50]. As chloral hydrate is a halogenated hydrocarbon, there is also an increased risk of ventricular arrhythmias due to increased catecholamine sensitivity. Compared to other available alternative products studied for insomnia related to atopic dermatitis, there is little room for continued use of chloral hydrate for this indication.

Doxepin

Tricyclic antidepressants such as doxepin have been used to treat insomnia for decades. Doxepin inhibits the reuptake of serotonin and norepinephrine by presynaptic neuronal membranes while also antagonizing histamine (H_1 and H_2) receptors [53]. As the tricyclic antidepressant with the greatest H_1 receptor antagonist activity, doxepin can be utilized as a sleep aid for patients with atopic dermatitis [5]. Evidence from clinical trials demonstrates that doxepin's combined H_1, H_2, and muscarinic antagonizing activities make it an effective option to treat chronic urticarial [54]. Furthermore, doxepin's high selectivity for the H_1 receptor has allowed it to earn FDA approval to treat insomnia [55]. Doxepin's sedative properties, combined with its anxiolytic and antidepressant effects, may be especially beneficial in patients who are depressed or anxious. However, the doxepin dose necessary for sleep aid is generally much lower than doses required to treat depression or anxiety. Low doses of doxepin (ranging from 1 mg to 6 mg) are effective in treating insomnia by facilitating sleep maintenance [56]. If higher doses are needed, nightly doses can be started at 10 mg in children and 25 mg in adults and titrated up based upon clinical response [5]. Doxepin is commercially available in various oral forms including capsules, tablets, and liquid concentrations.

Although sedating antidepressants are effective in facilitating sleep, tricyclic antidepressants are not considered to be first-line pharmacological therapy due to various toxicities. Doxepin is currently not FDA-approved for use in children. As an antidepressant, doxepin may increase the risk of suicidal ideation and behavior in children, adolescents, and young adults. Initiation of doxepin therapy warrants close observation for suicidality and unusual behavior changes. In addition to doxepin's serotonergic and antihistaminergic effects, it also possesses cholinergic and alpha-1 adrenergic receptor blockade activities. Adverse effects associated with doxepin therapy include headache, daytime sedation, hypotension, and xerostomia [56]. Although low-dose doxepin may be effective in facilitating sleep for up to 12 weeks, tolerance can develop to the sedating effects of tricyclic antidepressants [5]. Long-term administration of tricyclic antidepressants is associated with withdrawal effects upon discontinuation, which may cause rebound insomnia. Therefore, upon abrupt discontinuation of doxepin, patients should be cautiously monitored for sleep disturbances.

Montelukast

Leukotriene mediators are released from mast cells, eosinophils, and basophils and precipitate allergic conditions. Montelukast, a cysteinyl-leukotriene-1 receptor antagonist, is widely used to treat allergic rhinitis and asthma. While they are not the first-line therapy, leukotriene inhibitors are used as alternative or adjunctive therapies in children with asthma [57]. A systematic review including 11 clinical trials found leukotriene inhibitors to be as effective as antihistamines but less effective than intranasal corticosteroids in improving allergic rhinitis symptoms [58]. Montelukast may be especially beneficial in patients with concurrent asthma by reducing bronchospasm and diminishing the inflammatory response [59]. The enhanced leukotriene production observed in atopic dermatitis suggests that leukotriene receptor antagonism can be a potential treatment option for patients with atopic dermatitis [60]. However, data from randomized controlled trials have not shown any significant difference in efficacy between patients treated with montelukast compared to those treated with placebo [61]. Although not statistically significant, montelukast therapy demonstrated a modest decrease in daytime itching and sleep disturbances in children [62]. Children age 6 months to 5 years old are indicated to receive montelukast 4 mg daily, children between 6 and 15 years old should receive montelukast 5 mg daily, and children 15 years and older are indicated to receive montelukast 10 mg daily in the evening. Compared to other pharmacologic therapies, montelukast is not associated with any major adverse effects. Montelukast is generally well tolerated but can occasionally cause headaches and gastrointestinal symptoms such as diarrhea and abdominal pain. Convenient dosage formulations including tablets, chewable tablets, and oral packets help facilitate medication administration in children.

Benzodiazepines

Benzodiazepines are drugs frequently used to treat insomnia. They work to enhance the effects of gamma-aminobutyric acid (GABA) on the gamma-aminobutyric acid type A (GABA-A) receptor. The GABA-A receptor is a gated chloride channel that when activated allows chloride to enter into the cell inhibiting nerve transmission. As a class the benzodiazepines enhance GABA-A's inhibitory effects on the nervous system. Slight differences on the GABA-A receptor subtype, where different drugs bind, can lead to different clinical affects, i.e., sedative hypnotic versus anti-seizure [63–65].

There are five benzodiazepines officially approved for the treatment of insomnia (Table 28.2). The different pharmacokinetic properties of the approved drugs can dictate their best use in insomnia, for instance, drugs with quicker onsets and shorter half-lives would be more beneficial for patients having difficulty falling asleep. The longer elimination half-lives and active metabolites of some benzodiazepines could be more beneficial in patients who wake up during the night. However, these drugs can increase the likelihood of a prolonged hangover effect after waking up from sleep. Benzodiazepines are associated with a decrease in sleep latency and

Table 28.2 Benzodiazepine and non-benzodiazepines used for sleep

Benzodiazepine	FDA indication	Typical dose[a]	Peak concentration (h)	T 1/2 (h)	Dosage form	Comment
Estazolam	Yes	1–2 mg	2	10–24	1-mg and 2-mg tablets	Metabolized via CYP 3a4
Flurazepam	Yes	15–30 mg	1	2.3	15-mg and 30-mg capsules	Active metabolite has a longer t 1/2
Quazepam	Yes	7.5–15 mg	2	39	15-mg tablet	Active metabolite has longer t 1/2
Temazepam	Yes	7.5–30 mg	1.5	10–15	7.5-mg, 15-mg, 22.5-mg, and 30-mg tablets	
Triazolam	Yes	0.125–0.25 mg	1	1.5–5.5 h	0.125-mg, 0.25-mg tablets	Metabolized via CYP 3a4
Lorazepam	No	0.5–2 mg (Ref. [68])	2	12	0.5-mg, 1-mg, 2-mg tablets	Paradoxical reactions have been reported
Non-benzodiazepine hypnotics						
Zaleplon	Yes	5–20 mg	1	1	5-mg, 10-mg tablets	
Eszopiclone	Yes	1–3 mg	1	6	1-mg, 2-mg, 3-mg tablets	
Zolpidem	Yes	5–10 mg	1.6	2.5	5-mg, 10-mg tablets	Available as a solution, tablet, extended release tablet, sublingual tablet. Different dosage forms have different pharmacokinetic properties

Data from Refs. [63–65, 68]
[a]Dosing is based on adult data unless otherwise indicated.

significantly associated with increases in sleep duration. Benzodiazepines are associated with reports of daytime drowsiness and cognitive impairment versus placebo in studies [66, 67].

Non-benzodiazepine Hypnotics

Another class of drugs that works on the GABA-A receptor is referred to as the non-benzodiazepine receptor agonists; these drugs are also called the Z-drugs because the FDA-approved drugs include zaleplon, zolpidem, and eszopiclone. These drugs bind more selectively to the alpha subunit, which has been associated with the onset of sleep [68]. The time to peak concentration and the elimination half-lives of the Z-drugs are outlined in Table 28.2. They have shorter onsets and shorter durations, which coupled with their more specific binding could indicate a more favorable side effect profile as compared to the benzodiazepines, although side effects such as impairment of next-day cognition and somnolence have been reported [69, 70].

Benzodiazepine and non-benzodiazepine receptor agonist drugs may cause respiratory depression and should be used cautiously in patients with preexisting respiratory disease. The FDA has also issued a box warning on the concomitant use of benzodiazepines and opioids due to the risk of respiratory depression. The benzodiazepines and non-benzodiazepine receptor agonists are metabolized and cleared by the liver and kidneys, respectively, so it is advised to use them with caution in patients with renal or liver dysfunction [63, 78]. Additionally, long-term use of benzodiazepines can lead to dependence, and abrupt discontinuation can lead to withdrawal.

Topical Therapies

Topical therapies are generally considered first-line therapies for the treatment of atopic dermatitis. Goals of topical therapies include stopping the itch-scratch cycle, maintaining skin hydration, and minimizing factors that aggravate atopic dermatitis [71]. By achieving these goals, topical therapies may be beneficial in minimizing sleep disturbances in children. Topical therapies include emollients, corticosteroids, and calcineurin inhibitors.

Emollients moisturize the skin and restore skin integrity by inhibiting water loss and creating a protective barrier. Most emollients are available over-the-counter without a prescription and exist in several formulations including creams, lotions, and ointments; these agents commonly include mineral oil, petrolatum, ceramide, and urea as active ingredients [71]. Ceramide is a lipid found in the skin's stratum corneum and may improve pruritus and sleep in children with atopic dermatitis [72].

Topical corticosteroids interfere with antigen processing and suppress pro-inflammatory cytokines by acting on various immune cells including T lymphocytes, monocytes, macrophages, and dendritic cells [73]. Seven classes of topical steroids exist, ranging from the highest potency to lowest potency based on their vasoconstriction assays [74] (Table 28.3).

Some clinicians use short bursts of highly potent corticosteroids, while others utilize low potency agents and advance potency as needed for clinical response. Since children have a proportionately greater body surface area to weight ratio, the least potent corticosteroid should be utilized for long-term management. Highly

Table 28.3 Topical corticosteroids

Potency class[a]	Corticosteroid (%)	Formulation
1	Clobetasol propionate 0.05	Cream, ointment
	Halobetasol propionate 0.05	Cream, ointment
2	Betamethasone dipropionate 0.05	Ointment
	Desoximetasone 0.25	Cream, ointment
	Fluocinonide 0.05	Cream, ointment, gel, solution
3	Betamethasone dipropionate 0.05	Cream
	Betamethasone valerate 0.1	Ointment
	Fluticasone propionate 0.005	Ointment
	Triamcinolone diacetate 0.5	Cream
4	Hydrocortisone valerate 0.2	Ointment
	Mometasone furoate 0.1	Cream, ointment, lotion
	Triamcinolone acetonide 0.1	Ointment
5	Betamethasone valerate 0.1	Cream
	Fluticasone propionate 0.05	Cream
	Hydrocortisone butyrate 0.1	Cream, ointment, solution
	Hydrocortisone valerate 0.2	Cream
	Triamcinolone acetonide 0.025–0.1	Cream
6	Alclometasone dipropionate 0.05	Cream, ointment
	Desonide 0.05	Cream
	Fluocinolone acetonide 0.01	Cream, solution
7	Hydrocortisone 0.5–2.5	Cream, ointment, lotion

[a] *1* highest potency, *7* lowest potency

potent topical corticosteroids should not be utilized in children under 12 years old and should be limited to 1- to 2-week courses in patients with severe atopic dermatitis [74]. Most studies involve once or twice daily application of topical corticosteroids. Topical corticosteroid therapy is generally discontinued once symptoms improve; however, patients with frequent outbreaks may require maintenance therapy (e.g., once to twice weekly applications) to prevent relapses [73].

Topical corticosteroid therapy may result in systemic absorption, especially in children who receive highly potent therapies for longer durations. Systemic adverse effects associated with topical therapy are debatable but include hypothalamic-pituitary-adrenal axis suppression and growth suppression [74]. Local adverse effects include striae, petechiae, atrophy, acne, and rosacea. Due to the risk of systemic absorption, topical corticosteroid therapy should be used at the lowest potency to achieve clinical effect for the shortest duration possible. However, adrenal suppression is rare, and side effects of uncontrolled disease, such as short stature in atopic dermatitis, are more profound than chronic use of mid-potency topical steroids.

Calcineurin inhibitors are produced by *Streptomyces* bacteria and inhibit T-cell activation to block the production of pro-inflammatory cytokines and mediators that potentiate atopic dermatitis [73]. Topical calcineurin inhibitors include tacrolimus ointment and pimecrolimus cream. Pimecrolimus cream 1% is approved in children 2 years and older with mild to moderate atopic dermatitis. Tacrolimus 0.03% ointment is approved for children aged 2–15 years old with moderate to severe disease, while tacrolimus 0.1% ointment is approved for patients older than 16 years old

[74]. These therapies are generally applied to the affected areas once or twice daily. Although systemic exposure to topical calcineurin inhibitors is minimal, the FDA has issued a black box warning for the theoretical risk of malignancy based on the therapy's mechanism of action. Common adverse effects include local reactions such as stinging and burning, which occur more frequently than topical corticosteroid therapy [73]. Topical calcineurin inhibitors are generally reserved as second-line therapy for cases of atopic dermatitis that are refractory to topical corticosteroids.

Intranasal Corticosteroids

Corticosteroids are effective in treating allergic rhinitis by significantly reducing mediator and cytokine release and inhibiting the recruitment of basophils, eosinophils, neutrophils, and mononuclear cells within the nasal mucosa [27]. Intranasal administration of corticosteroids enables high drug concentrations to be achieved locally, while minimizing systemic adverse effects. In a systematic review, intranasal corticosteroids provided greater relief than oral antihistamines in relieving nasal symptoms including blockage, sneezing, and itch [75]. Various formulations of intranasal corticosteroids are available over-the-counter. Triamcinolone (110 mcg/spray) and mometasone (50 mcg/spray) are both indicated for children older than 2 years old at a starting dose of one spray per nostril once daily. Fluticasone propionate (50 mcg/spray) is indicated for use in children 4 years and older at a dose of one spray per nostril once daily; children older than 12 years old may use up to two sprays per nostril once daily. Patients should gently blow their nose prior to administration and tilt their head forward when administering the dose. Adverse effects associated with intranasal corticosteroids include nasal irritation, epistaxis, pharyngitis, headaches, and smell/taste disturbances. Due to the low bioavailability of intranasal glucocorticoids, systemic adverse effects such as hypothalamic-pituitary-adrenal axis suppression and growth impairment are not expected [59].

Inhaled Corticosteroids

Asthma is one of the most prevalent chronic respiratory disorders in childhood. A previous study found that children who experience more frequent asthma symptoms experience greater daytime somnolence and tiredness than children with well-controlled asthma [76]. Inhaled corticosteroids are the most effective pharmacologic therapies for long-term management of asthma. Corticosteroids attenuate the underlying inflammation observed in asthma by reducing airway hyperresponsiveness and inhibiting inflammatory cell migration and activation [57]. Inhaled corticosteroids reduce airway impairment and reduce exacerbations, but they do not alter the progression or underlying severity of asthma in children.

Beclomethasone, budesonide, flunisolide, fluticasone, mometasone, and triamcinolone acetonide are administered at low, medium, and high comparative daily dosages, based upon the patient's asthma severity [57]. Inhaled corticosteroids are available as metered-dose inhalers (MDI) and dry powder inhalers (DPI). MDI should be administered via slow and deep inhalations, followed by a 10-second breath hold. In contrast, DPI inhalations involve rapid and deep inhalations. Inhaler spacers or valved holding chambers may be utilized to facilitate administration of metered-dose inhalations in young children. Nebulized corticosteroids, administered via slow tidal breathing, are alternatives for children who are unable to use MDI or DPI. Children should be instructed to rinse their mouths following corticosteroid administration to reduce the risk of thrush. Other common adverse effects include cough and dysphonia; systemic adverse effects (e.g., adrenal suppression, growth suppression, skin thinning, and osteoporosis) occur with high daily doses that are used chronically [57]. Long-term studies have found growth may be stunted with prepubescent use of medium potency inhaled corticosteroids for asthma, so risks/benefits should be considered [77].

Immunomodulatory Therapies

Calcineurin Inhibitors and Antimetabolites

In severe and refractory cases of asthma or AD, immunomodulatory medications may need to be initiated to help control pruritus and improve sleep [18]. Cyclosporine, tacrolimus, azathioprine (AZA), and mycophenolate mofetil (MMF) are all potent immunosuppressive agents most commonly used to prevent organ rejection after transplant. Cyclosporine (CSA) and tacrolimus (TAC) are calcineurin inhibitors (CNIs) that block interleukin-2 transcription and thus prevent T-cell activation. Studies have shown that a short course of cyclosporine can reduce AD symptoms and improve quality of life [18]. CSA doses ranged from 2.5 to 5 mg/kg/day. Due to the side effect profile of nephrotoxicity, hypertension, diabetes, infections, and even cancer, CSA and TAC are not recommended as first-line therapy. According to AD guidelines, there is currently insufficient evidence to recommend systemic CNIs for the management of AD [7].

Both AZA and MMF are antiproliferative agents that have reported use in severe AD. Azathioprine is a prodrug that is quickly converted in vivo to 6-mercaptopurine and then to the active metabolites 6-thioguanine nucleotides [78]. 6-Thioguanine nucleotides disrupt both the salvage and de novo DNA and RNA synthesis, resulting in nonspecific cell cycle arrest at the G2-M phase. Leukopenia, anemia, and thrombocytopenia are common and often dose-dependent side effects observed with AZA. Less common side effects of AZA include skin cancer, hepatotoxicity, and pancreatitis. It is important to note that baseline thiopurine methyltransferase (TPMT) levels must be checked prior to AZA initiation. If TPMT levels return low or undetectable, then AZA is contraindicated due to the risk of profound

myelosuppression. The typical dosing range for AZA is 1–3 mg/kg/day and 2.5 mg/kg/day being the most common reported dosage in pediatric AD patients [7].

MMF inhibits lymphocyte proliferation more specifically than AZA. By inhibiting inosine monophosphate dehydrogenase (IMPDH), an enzyme required for the de novo synthesis of purines, MMF selectively inhibits lymphocyte proliferation [78]. Unlike other cell lines, T and B lymphocytes are unable to utilize salvage pathways for purine synthesis. The most common reported side effects include diarrhea and dose-dependent myelosuppression. In a retrospective analysis of 14 children with severe AD not responsive to treatment, majority of patients treated with MMF responded to therapy (4 achieved complete clearance, 4 achieved 90% improvement, 5 achieved 60–90% improvement, and 1 experienced treatment failure) [18]. On average patients responded within 4 weeks of therapy with MMF doses of 20–25 mg/kg/dose twice daily in younger children and 15–20 mg/kg/dose twice daily in adolescents. According to AD guidelines, MMF is a safe systemic alternative option for pediatric patients with refractory AD [7]. However, given its immunosuppressive properties, clinicians should monitor for infections and malignancies in patients who remain on long-term therapy.

Systemic Corticosteroids

The immunosuppressive effects of corticosteroids alter different pathways at the transcriptional level, which enable them to treat various allergic conditions. In asthma, short courses of systemic corticosteroids are used to promptly control asthma exacerbations; in patients with severe persistent asthma, systemic corticosteroids may be utilized for long-term management [57]. In acute asthma exacerbations, intravenous methylprednisolone or oral prednisolone and prednisone are administered at doses of 1–2 mg/kg/day in two divided doses. Inflammatory cytokines and other mediators directly cause sleep disturbances in children with atopic dermatitis [1]. Although systemic corticosteroids are FDA-approved for the treatment of atopic dermatitis, there is poor evidence supporting the efficacy of systemic corticosteroid therapy in treating atopic dermatitis in children [79]. Prednisolone sodium phosphate is FDA-approved for the treatment of allergic skin disorders in children at a dose of 0.14–2 mg/kg/day in divided oral doses. Although systemic corticosteroids have potent anti-inflammatory properties, they are not routinely recommended for the treatment of allergic rhinitis due to adverse effects and lack of superiority over inhaled formulations [59]. Adverse effects include mood disturbances, gastrointestinal symptoms, weight gain, fluid retention, hypernatremia, hyperglycemia, hypothalamic-pituitary-adrenal axis suppression, immunosuppression, and poor wound healing. Systemic corticosteroid therapy may also exacerbate sleep disturbances by causing insomnia. Doses should be administered in the morning to lessen this risk. Due to the risk of adrenal suppression, systemic corticosteroid doses should be weaned until discontinuation if therapy is continued for greater than 1 week [71].

Systemic corticosteroid therapy is generally reserved for severe allergic conditions that are refractory to other pharmacotherapies, due to its various toxicities.

Biologic Agent

Dupilumab is an anti-interleukin (IL)-4 receptor human monoclonal antibody that is indicated to treat atopic dermatitis by inhibiting type 2/Th2-mediated inflammation [80]. The therapy is currently FDA-approved for adult patients with moderate to severe atopic dermatitis who are not adequately controlled with topical therapies. Doses are administered subcutaneously with an initial 600 mg dose followed by a 300 mg maintenance dose injected once every other week. Injection site reactions and conjunctivitis are common adverse effects associated with dupilumab therapy. At the time of writing this book, dupilumab has not yet been approved for use in children with atopic dermatitis.

Pregnancy and Lactation Considerations

Table 28.4 demonstrates the safety of the aforementioned pharmacological therapies in pregnancy and lactation as categorized by the FDA [81, 82]. According to the US FDA pregnancy category considerations, category A drugs are the safest since controlled studies in women failed to demonstrate fetal risk, and the possibility of fetal harm has not been demonstrated. Category B refers to drugs that have not shown fetal risk in animal reproductive studies, but there are no controlled studies in pregnant women. Category C classification refers to drugs that have revealed fetal animal harm, but no studies in pregnant women exist or studies in women and animals are not available. Category D medications have evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk for life-threatening conditions where alternative medications are unavailable. Lastly, category X drugs have demonstrated fetal adverse effects in humans, and the risk of using the drug is not worth any benefits obtained from the drug.

Despite these FDA categories, clinicians should be advised that many of these medications have not been studied in pregnancy and that the FDA pregnancy categories oversimplify the risk. For example, mycophenolate mofetil is given a category D rating, but most guidelines and clinicians would agree that it is absolutely contraindicated in pregnancy, as there are other immunosuppressive options on the market. Furthermore, the use of benzodiazepine and benzodiazepine receptor agonists may increase the risk of premature delivery and low birth weight infants, but current FDA pregnancy rating system does not portray these risks [83]. To combat this problem, the FDA proposes that by June 2020 all prescription drugs will be subject to a new pregnancy-labeling requirement.

Table 28.4 Pregnancy and lactation considerations

Drug	FDA pregnancy category ([a]unless otherwise noted)	Lactation safety
Antihistamines		
Diphenhydramine	B	Infant risk cannot be ruled out
Hydroxyzine	C	Infant risk cannot be ruled out
Cetirizine	Inconclusive, fetal risk cannot be ruled out	Infant risk cannot be ruled out
Loratadine	B	Maternal medication usually compatible with breastfeeding
Desloratadine	C	Infant risk cannot be ruled out
Fexofenadine	C	Maternal medication usually compatible with breastfeeding
Levocetirizine	Inconclusive, fetal risk cannot be ruled out	Infant risk cannot be ruled out
Benzodiazepines		
Estazolam	X	Infant risk cannot be ruled out
Flurazepam	C	Infant risk cannot be ruled out
Quazepam	X	Infant risk cannot be ruled out
Temazepam	X	Infant risk cannot be ruled out
Triazolam	X	Infant risk cannot be ruled out
Lorazepam	D	Maternal medication usually compatible with breastfeeding
Non-benzodiazepine hypnotics		
Zaleplon	C	Infant risk is minimal
Eszopiclone	Inconclusive, fetal risk cannot be ruled out	Infant risk cannot be ruled out
Zolpidem	Inconclusive, fetal risk cannot be ruled out	Maternal medication usually compatible with breastfeeding
Immunomodulatory therapies		
Prednisolone	C	Maternal medication usually compatible with breastfeeding
Dupilumab	Inconclusive, fetal risk cannot be ruled out	Infant risk cannot be ruled out
Tacrolimus	Inconclusive, fetal risk cannot be ruled out	Infant risk cannot be ruled out
Cyclosporine	C	Infant risk cannot be ruled out
Azathioprine	D	Avoid breastfeeding, infant risk cannot be rules out
Mycophenolate mofetil	D fetal risk has been demonstrated	Infant risk cannot be ruled out
Others		
Melatonin	Inconclusive, fetal risk cannot be ruled out	Infant risk cannot be ruled out
Doxepin	C	Infant risk has been demonstrated
Montelukast	Inconclusive, fetal risk cannot be ruled out	Infant risk cannot be ruled out
Clonidine	C	Milk effects are possible
Chloral hydrate	Unknown[a]	Excreted in breast milk

[a]Animal reproduction studies have not available. Chloral hydrate crosses the placenta and withdrawal symptoms possible in the neonate.

Conclusions

Treatment of SD in patients with allergic diseases is important to prevent long-term serious consequences such as neurocognitive decline, impaired, growth, and reduced quality of life. Topical therapies are considered first-line therapies for the treatment of atopic dermatitis but may not always treat SD. Inhaled and intranasal therapies prevent the risk of systemic side effects but may not always provide full symptom relief. Sedating antihistamines are an option for children who are at least 2 years of age who suffer from SD. However, treatment should be limited to 1–2 weeks. Low melatonin levels have shown lower sleep efficiency in patients with AD, and melatonin supplementation may provide benefit in patients with SD. Clonidine is another sedative agent that may be an option in patients with SD, but due to its toxicity profile, clinicians may want to reserve this treatment option for patients with concomitant hypertension or ADHD. Doxepin, a tricyclic antidepressant, may be an option for patients who suffer from anxiety or depression as well as insomnia. However, doxepin lacks pediatric FDA approval, and risks of suicidal behaviors along with a variety of side effects mentioned earlier prevent it from first-line use. If looking for an agent with minimal side effects, montelukast, a leukotriene receptor antagonist, may be an option as studies have demonstrated enhanced leukotriene production in allergic diseases. Selected benzodiazepines have FDA approval for sleep but have not been studied in insomnia associated with allergic diseases. Lastly, there is currently limited evidence to use immunomodulatory therapies for treatment of SD in children with allergic diseases.

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29 Alternative/Integrative Medical Approaches in Allergy and Sleep: Basic Principles and Clinical Practice

Xiu-Min Li, Henry Ehrlich, Paul Ehrlich, Anne Maitland, Erin Thanik, Julia A. Wisniewski, and Danna Chung

Allopathic physicians in increasing numbers are combining treatments from older systems such as Chinese and Ayurvedic medicine, where traditions emphasize mind-body harmony including balanced diet, moderate behavior, exercise, and respect for circadian rhythms, with their more conventional practices. The combination is referred to as integrative medicine. The incorporation of the practice of integrative medicine is facilitated by the fact that it does not necessitate learning the alternative vocabulary and anatomical theories of the older tradition to practice methods of treatment. Increasingly, more active interventions in the form of acupuncture and herbal medicine are gaining popularity as part of this integrative practice for a wide variety of illnesses, including chronic conditions such as allergies, asthma, and disordered sleep (which can be a by-product of atopy as well as behavioral issues such as stress and anxiety). Interest in acupuncture, herbal medicine, and other modalities has grown, attracting research to elucidate knowledge of

X.-M. Li (✉)
Department of Pediatrics, Pediatric Allergy and Immunology, Jaffe Food Allergy Institute, Center for Integrative Medicine for Immunology and Wellness, Icahn School of Medicine at Mount Sinai, New York, NY, USA
e-mail: xiu-min.li@mssm.edu

H. Ehrlich
Pediatric Allergy and Immunology, Jaffe Food Allergy Institute, Center for Integrative Medicine for Immunology and Wellness, Icahn School of Medicine at Mount Sinai, New York, NY, USA

P. Ehrlich
Department of Pediatrics, New York University Langone Medical Center, New York, NY, USA

A. Maitland · D. Chung
Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

E. Thanik · J. A. Wisniewski
Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA

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therapeutic mechanisms as well as proof of efficacy. This chapter will first discuss the background of complementary and alternative medicine (CAM) and traditional Chinese medicine (TCM) in the United States with a focus mainly on TCM practices for allergic diseases. It will also discuss the frequent correlation of disordered sleep with allergic diseases, given that atopy can affect breathing, pruritis, and allergic mediators such as the release of histamine, which is important to keeping us awake during the day but can hinder the length and quality of sleep when released at night.

Complementary and Alternative Medicine in the United States

CAM is a group of diverse medical and health-care systems, practices, and products not considered part of conventional medicine. They range from highly organized systems, such as TCM, that are complete with their own literature to more singular practices such as meditation. Integrative medicine combines conventional and CAM treatments for which there is evidence of safety and effectiveness [1]. CAM in the United States is particularly popular to achieve wellness and treat certain chronic conditions. In December 2008, the National Center for Complementary and Alternative Medicine (NCCAM) and the National Center for Health Statistics (part of the Centers for Disease Control and Prevention) released new findings on Americans' use of CAM [2]. The survey of 23,393 adults aged 18 years or older and 9417 children aged 17 years and under found that 38% of adults and 12% of children had used CAM in some form during the 12 months prior to the survey [3]. The survey sampled people of all backgrounds. Adult use is greater among women and those with higher levels of education and income. This is consistent with the previous survey [3]. CAM includes natural products such as herbal medicines, vitamins, and probiotics and mind-body therapy such as acupuncture, acupressure, cupping, and qigong. In a 2010 publication, six in ten Americans reported using dietary supplements, and one in six Americans reported using herbal remedies on a regular basis [4]. CAM is often employed concurrently with conventional practices, however, as 75% of CAM users also reported using at least one prescription drug. In contrast, the World Health Organization estimates that 80% of people worldwide rely on traditional medicine for primary health care [5].

CAM may represent a source of savings to the health-care system as well as a therapeutic breakthrough for stubborn diseases. As such, they may be recognized by payers under innovative programs at the state level. This is highlighted by 2016 federal regulations granting states to allow Medicaid managed care plans to provide their enrollees with "in lieu of services—alternative services or settings not included in the State Plan but [that] are medically appropriate, cost-effective substitutes for covered services or settings" [6].

Traditionally, US medical schools have not provided education on CAM therapies. However, medical schools have begun to incorporate elements of CAM and integrative medicine into their curricula. Many major hospitals including

Yale, Northwestern University, University of North Carolina, Harvard, and Tufts, as well as Mount Sinai, have added integrative clinical programs. Some institutions have added training programs to credential conventional practitioners/physicians for integrative holistic medicine or acupuncture so that the conventional physicians and health providers can directly provide CAM for their patients. As an example, Mount Sinai Beth Israel has created a fellowship for acupuncturists to work with patients to avoid relying on analgesics for postoperative pain. These collaborations between CAM and conventional health-care providers may create a new structure of integrative and complementary services to treat conditions such as eczema, asthma, allergic rhinitis, and food allergy among others.

Traditional Chinese Medicine and New Drug Discovery

TCM is defined as a medical system that primarily uses Chinese herbal medicines, acupuncture, and acupressure. Two principal tools are used by practitioners of Chinese medicine. The first is herb-based medicines, often in combination with one another in "classic" formulas that are more effective than their component parts alone. The second is acupuncture done with needles placed in identified points on the body and its subsidiaries: acupressure, in which pressure is applied to the points with no penetration, and moxibustion, in which heat is applied to the points.

TCM has a long history and is part of mainstream medicine in mainland China, Hong Kong, Taiwan, Japan, and Korea where the costs are normally covered by insurance. In these Asian countries, Chinese herbal medicines are used in health care and also are resources for new drug discoveries. Integrative practice and research with Western medicines are well established in these countries but are now gaining international recognition. In 2015, a Nobel Prize in Medicine was given to Dr. Tu Youyou, Chinese medicine pharmacologist, for her work in deriving an antimalaria medicine, *Artemisia annua* from Chinese herbal medicine Herba Artemisiae Annuae (Qin Hao).

TCM is a major CAM modality in the United States and is beginning to play a role in the health-care system as a stand-alone or integrative practice. Unlike Asia, the European Union, and the United Kingdom [7], Chinese herbal medicines in the United States are classified as dietary supplements [8]. In 2004, the US Food and Drug Administration (FDA) provided guidance for investigating botanical drug products including formulas comprised of multiple herbal constituents [8]. Although preclinical and clinical studies are limited, several of these suggest that TCM herbal formulas may have potential for treating food allergies [9, 10].

Of note, acupuncture has been increasingly employed for pain, which likely improves sleep quality [11]. In fact, the US Army has been seeking alternatives for active-duty soldiers and veterans for chronic pain, including acupuncture. Regulators have already shown greater receptivity to acupuncture and herbal medicines to treat pain and it is possible that this will extend to chronic conditions such as sleep

deprivation and allergy, where pharmaceutical drugs have issues of their own. They have given greater credence to the centuries of safe and effective use by practitioners in Japan, Korea, and China, although the standard of science in those countries must further align with those in the West, a process that is well underway.

Complementary and Alternative Medicine Use mong Allergy Practices

Complementary and alternative practices in the field of allergy and immunology are also becoming more common. In 2009, the Complementary and Alternative Practices Committee of the American Academy of Allergy, Asthma, and Immunology (AAAAI) reported findings of a national survey of allergy specialists. This survey focused on the attitudes of academy members toward CAM. It found that 80% of respondents were interested in learning more about CAM [12]. In 2016 [13], the survey of academy members reported that their patients had used herbal medicines (67.6%), vitamins (61.9%), probiotics (57.7%), fish oil/omega-3 (57.7%), or *Echinacea* (38.0%). Many also used acupuncture (57.1%), yoga (52.1%), prayer (48.6%), meditation (41.4%), relaxation (39.7%), deep breathing (33.3%), massage (48.5%), and spinal manipulation (42.8%). The least used modalities were homeopathy (36.2%), home remedies (25.7%), Ayurveda (18.2%), folk care (15.4%), qigong (12.7%), and energy (12.5%). Approximately 90% noted a desire to use natural products and 75.4% because of recommendations from friends, family, or media, whereas 62.3% were fearful of conventional therapies and 58% believed CAM to be safer.

The most common indications for CAM use were allergic rhinitis (76.8%), overall health and well-being (71.0%), asthma (60.9%), eczema (58.0%), and allergy prevention (42.0%). Use of CAM remedies for food allergy (53.6%) rose dramatically from 2002 (11%) [14]. The reasons for the increase observed with food allergy in particular are unknown. It might be due to the different survey populations (practitioners vs patients/families), lack of satisfactory conventional treatment for food allergy, experience of CAM modalities, or the increased incidence, knowledge, and scientific evidence about food allergy over the past 10 years.

The Complementary and Alternative Practices Committee of the AAAAI provides resources such as the Natural Medicines Comprehensive Database (NMCD). The 2016 survey found that 99% of respondents wanted a "trustworthy internet accessible resource for checking ingredients, side effects, interactions, and evidence based efficacy data," supporting the need for reputable databases.

In summary, CAM use is becoming common among patients with allergy or in the field of allergy practice. In response, US training programs and medical schools will need to educate future practitioners about CAM therapies and develop guidelines to assist clinicians. It is likely that a growing number of allergists/immunologists will manage patients with both conventional and CAM therapies to provide more efficient service, prevent adverse reactions, and remedy conventional compliance failures.

Traditional Chinese Approaches in Allergy

Acupuncture and Asthma

Asthma is a major economic and social burden for the United States, amounting to $82 billion annually according to the most recent figures compiled by the American Thoracic Society for the years 2008–2013, representing medical expenses and costs associated with work, school absences, and death. This assessment included 8.7 million workdays and 5.2 million school days lost due to asthma, which is likely due in some part to loss of sleep from active symptoms contributing to this absenteeism [15]. This excludes "presenteeism," a lack of productivity, attentiveness, and vigorous participation among those who go to work and school.

Acupuncture has a long tradition of use for treating asthma. Traditional Chinese medicine has recognized a complex list of disease phenotypes for centuries including "wind-cold type," "phlegm heat type," and "lung deficiency. These may equate to Western terminology such as "acute asthma episode," "recovering phase," and "chronic asthma." Treatment involves tailored acupuncture to the organ systems believed to be involved, moxibustion (heat applied to acupuncture points), and administration of herbal medicines [16, 17].

The record of successful treatment of asthma using acupuncture in Western studies is mixed, but several research articles show promise. One murine study showed serum regulation of ovalbumin-specific IgE, along with IL-17A, IL-17F, and IL-22 in response to acupuncture [18]. In a clinical study, acupuncture patients showed improved CD3+ cells and CD4+ cells and decreased IL-6 and IL-10 [19]. A Danish study of 52 preschool children (26 intervention, 26 controls) showed that among the subjects treated with acupuncture ten times over 3 months, "Significant reductions were observed in subjective asthma symptoms and in use of inhaled steroids (IHS) and β(2) agonists in both groups at 3 mo. Compared with the control group, the reduction in asthma symptoms (P = .0376) and use of IHS (P = .0005) was significantly larger in the intervention group." It must be noted that the gains didn't last long past the cessation of treatment indicating that acupuncture, as with inhaled corticosteroids, may require maintenance therapy [20].

Chinese Herbal Medication for Asthma

Anti-asthma simplified herbal medical intervention (ASHMI) is a three-herb formula ling-zhi (*Ganoderma lucidum*), ku-shen (Radix *Sophora flavescentis*), and gan-cao (Radix *Glycyrrhiza uralensis*), developed after experiments with various classic formulas.

In a human trial at Weifang Asthma Hospital in China, 92 atopic, nonsmoking patients (43 men and 49 women, age 18–65 years) met the criteria of moderate-severe, persistent asthma and were randomly assigned to receive ASHMI or prednisone with 46 subjects to each group. The ASHMI group received oral ASHMI

capsules (four capsules, three times a day) and placebo tablets similar in appearance to prednisone. Subjects in the prednisone group received oral prednisone tablets (20 mg once a day in the morning) and placebo capsules for 4 weeks. By most efficacy measures, the two groups were comparable—symptom reduction, lowered IgE levels, and peripheral eosinophil levels. However, peripheral blood studies of ASHMI subjects showed no deficit in adrenal function. Numerous studies have shown that IL-4, IL-5, and IL-13 secretion after repeated antigen exposure is the major driving force behind persistent allergic asthma. ASHMI treatment significantly reduced serum IL-13 and IL-5 levels, while, unlike prednisone, they increased IFN-γ [21].

Building on the promising results at Weifang, a US FDA Phase I study was initiated to evaluate the hematologic tolerability and safety of ASHMI. Twenty subjects (12 on ASHMI and 8 on placebo) completed the study. Subjects were started on ASHMI or placebo twice daily with meals for 7 days. They continued their conventional asthma medications throughout the study but were asked to refrain from other herbal medications. No ASHMI patients had grade 3 adverse effects, but three in the placebo group did. Four subjects (33%) treated with ASHMI and four placebo-treated subjects (50%) reported gastrointestinal symptoms [22].

Furthermore, substantial murine and in vitro studies have shown promising results, such as inhibition of airway smooth muscle contractions and low levels of cytokines IL-4, IL-5, and IL-13, which accompany uncontrolled asthma [23]. Other studies have isolated the active ingredients [9], for example, flavonoids found in *Glycyrrhiza uralensis* (Chinese licorice), which inhibit the release of eotaxin, a chemoattractant for eosinophils that are elevated in inflamed airways that rebound steeply after prolonged steroid use. An in vitro study showed that co-treatment of lung fibroblasts with the Chinese licorice flavonoid and steroids prevented the paradoxical effect of steroid on eotaxin production following long-term culture [24].

These results also make ASHMI a candidate for mitigating the symptoms of asthma, one of which is disordered sleep. In addition, where ASHMI can be used as a clinical treatment supplement in concert with other herbal medicines and sometimes acupuncture or acupressure, it has also provided long-term relief from nasal and lower respiratory symptoms among patients with significant comorbidities such as food allergies, eczema, and eosinophilic esophagitis.

Chinese Herbal Medicine and Food Allergy (Food Allergy Herbal Formula, FAHF-2)

Chinese herbal medicines have been used for hundreds and even thousands of years for symptoms that suggest their utility for atopic conditions. For example, a promising nine-herb treatment for food allergies called FAHF-2 (Food Allergy Herbal Formula, version 2) and its refined successor versions called B-FAHF-2 and E-B-FAHF-2 were derived from a ten-herb formula called *Wu Mei Wan*, which for thousands of years was used for intestinal parasites. FAHF-2 is the first US FDA botanical investigational new drug (IND) for food allergy. Substantial scientific research demonstrated that FAHF-2 and refined FAHF-2 products provide

long-term protection against anaphylaxis in peanut- and multiple-food-allergy models. Clinical studies demonstrated safety and preliminary beneficial immunomodulatory effects on T cells and basophils. Studies also began to identify the active compounds from FAHF-2 and other herbal medicines to provide additional avenues for developing botanical drugs for treating food allergy and related inflammatory conditions.

Chinese Herbal Medicine for Frequent and Potentially Severe Food Allergy (FSFA)

One of the disadvantages for certifying TCM to regulatory standards is that the worst cases are characterized by complex comorbidities, particularly with food allergies. Practice-based evidence (PBE) studies that use existing treatment are an alternative to randomized controlled trials and well-suited to determine what works best for specific patient types in day-to-day clinical practice. They can provide a holistic picture of patients, treatments, and outcomes seen in real-world settings. They can uncover better practices more quickly than randomized trials, while achieving many of the same advantages. TCM is inherently an individualized approach using Chinese herbal medicines as well as acupuncture and acupressure; PBE studies are well suited to define what TCM therapies will be the best for the specific group of patients with food allergies.

This approach was the basis of a study of three patients with diagnosed severe food allergy (as documented by allergist-determined history of allergic reactions to food allergen, a positive skin test result, and/or elevated food allergen-specific IgE level), clinical reactions that became worse over time prior to TCM treatment, FSFA including multiple life-threatening episodes (>10 reactions and >2 epinephrine uses in the 3 months prior to starting TCM therapy), adherence to the TCM regimen, and completion of at least 6 months of TCM therapy [25]. In this study, therapy consisted of oral formulas, baths and creams, and some additional herbs for individuals. Acupuncture/acupressure was also administered during clinic visits. All three patients were able to achieve substantial normalization of diets and activities.

Herbal Medicine and Eczema

Atopic dermatitis may contribute more directly to the vicious cycle of stress and disordered sleep than any other atopic disease. When a child is the patient, ramifications extend to the whole family. An article in *JAMA Pediatrics* notes “Atopic dermatitis often appears during the first months of life when sleep patterns are being established. Although approximately 10% to 30% of all children experience difficulties with sleep during the first few years of life, sleep disturbances are increased in children with AD because of itching and scratching, which interfere with the initiation and maintenance of sleep. Comforting behavior, learned associations, and habits influence the development of sleep patterns; in AD, itching and scratching

become the association and behavior that disturbs sleep. …[S]leep patterns of the family of an affected child are likely disturbed, as parents awake to comfort or treat the children's symptoms" [26]. Kahan et al. posit that sleeplessness damages collagen production, impairing barrier function and damaging mucous membranes [27]. Eczematous patients start at a disadvantage to those whose disordered sleep precipitates breakdown in skin integrity. Impaired skin and itching contributes to sleeplessness, which in turn can exacerbate skin impairment.

CAM treatment for eczema is not as well studied as for asthma. Patients have explored alternative treatments from weaving silver and silk thread into garments for daily use, to biofeedback and hypnotherapy and bathing in the Dead Sea [28]. Traditional Chinese medicine has shown great promise in clinical practice, although treatment is not as straightforward as taking daily ASHMI capsules. Like FAHF-2 this protocol is taken from ancient sources, namely, Tang Dynasty (618–906ce) treatments for burns from that era's numerous wars.

A retrospective study by Wisniewski et al. enrolled 14 patients ranging in age from 6 months to 52 years, with a median age of 5.4 years. Baseline levels on the Dermatology Quality of Life Index (DQOL) ranged from 10 to 30, with a median score of 17. The SCORAD index showed a range from 42 to 103, with a median of 89, and 13 out of 14 were above 50. There were three avenues of therapy: an internal remedy, several external compounds, and acupuncture. To test safety, the herbal preparations were fed to mice at levels 24 times the human doses with no adverse effects [29]. The internal remedy was *Erka Shizheng* Herbal Tea, in practice called *Shi Zhen* tea, an extract of nine herbs. External TCM remedies included a bath additive containing eight individually extracted herbs. The patient was instructed to soak in the bath with the additive for 20–30 min a day, and a TCM herbal cream was applied to the skin, two to three times a day.

Half of the included patients had been treated intermittently with oral corticosteroids before starting TCM treatment, including five who had taken oral steroids in the previous 3 months. Over the course of treatment, 69% of patients reported stopping topical steroids, 80% stopped oral steroids, and 80% stopped antihistamines.

Three patients had used stronger immune suppressants, such as cyclosporine, although only one was doing so at the time of starting TCM; this was discontinued by 3 months. Five patients had tried other types of alternative therapies prior to their referral for TCM. While all patients reported histories of food allergy, only 10 of the 14 of patients reported managing their eczema by avoiding foods. Some foods were successfully reintroduced over the study period, although no patient could follow a completely unrestricted diet. Severity of disease and quality of life improved measured by both SCORAD and DLQI. During the first 3 months of treatment, seven patients experienced 60–90% improvement (classified as "good") and sustained it over 3–15 months of follow-up. One patient achieved excellent improvement (>90%) in the first 3 months, which was sustained for 5.4 months, the last report before the study concluded. Seven patients showed inadequate (<60%) improvement in SCORAD in the first 1–3 months but attained good or excellent improvement over the following 3–15 months. At the end of the study period, 12 patients had sustained good (>60%) improvement, and 5 out of 14 had sustained excellent

improvement (>90%). Improved quality of life, especially improvements in sleep and pruritus, was observed sooner than improvements in skin quality and SCORAD. Eleven of 14 patients experienced at least a 50% improvement in quality of life during the first 1–3 months of therapy. At the end of the study period, 12 of 14 patients reported sustained improvement in quality of life with 10 of 14 reporting >80% improvement (Fig. 29.1). Peripheral eosinophilia decreased from 1000 ± 700 mc/L to 500 ± 200 ($P = 0.03$) with no change in total blood counts. Baseline total IgE was available for 12 of 14 patients, and subsequent total IgE values were available for 10 of those 12 patients. A decreasing trend in total IgE was observed in seven patients. All patients tolerated the TCM treatment.

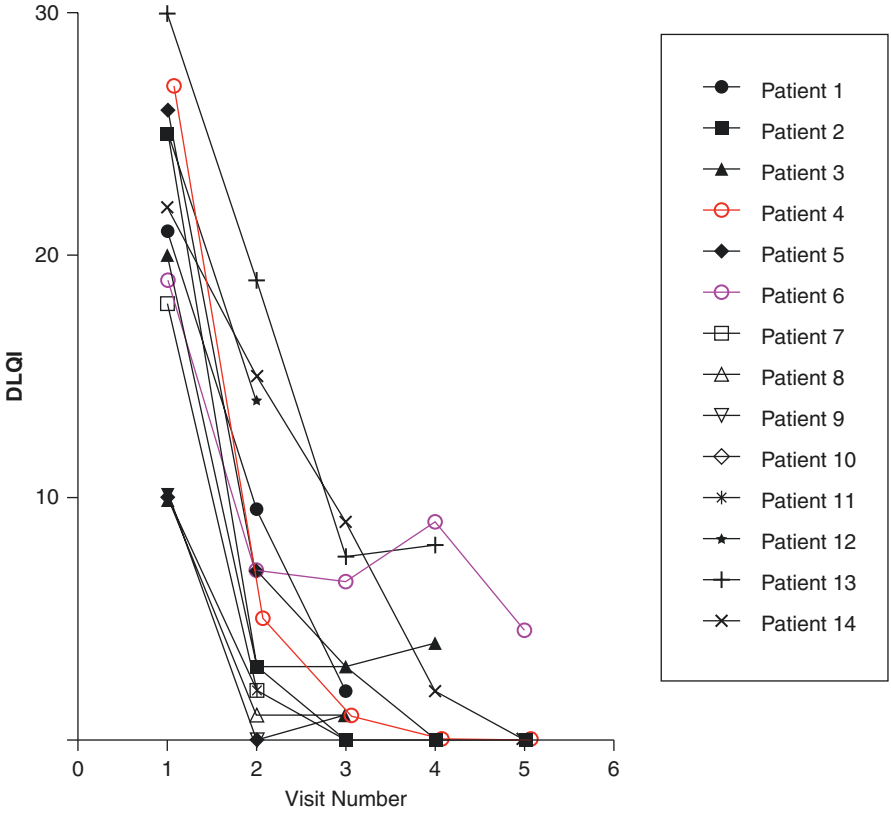


Fig. 29.1 Improvement of impaired quality of life. Dermatology Life Quality Index (DLQI) scores before and after TCM: DLQI scores from onset of TCM treatment (visit 1) through 8 (IQR 3–24) months of treatment (visit 2–5). The Dermatology Life Quality Index (DLQI), a validated survey comprised of ten questions for assessment of the impact of skin diseases on patients' lives, was used to measure health-related quality of life. Each DLQI question is scored on a scale of 0 (nothing) to 3 (severe) for a maximum total score of 30, representing the highest impairment to life quality. There are market improvements (reduction) of DLQL scores ($P < 0.0001$)

Acupuncture and Eczema

While acupuncture alone may not cure itching, it can serve as an important adjuvant to topical and systemic steroids and antihistamines that are standard of care with eczema. Small clinical studies of acupuncture and eczema have borne out the clinical efficacy reported by patients and practitioners, and there is a small body of scientific evidence to unveil the mechanisms behind it.

Florian Pfab et al. showed that acupuncture significantly reduced histamine-induced itching [30]. This same research group studied the effect of acupuncture on ten patients with atopic eczema for itch intensity and in vitro basophil CD63 expression after exposure to a pollen and dust mite allergens and compared them to an untreated control group. The results showed both reduced itch intensity and in vitro allergen-induced basophil activation [31]. More studies may indeed make acupuncture a welcome addition to standard of care.

CAM and Environmental Allergy

The most common form of atopic disorder is allergic rhinitis [AR]. This disorder can also disrupt sleep given discomfort due to symptoms including nasal congestion, cough, and breathlessness. The market for herbal AR remedies is dominated by over-the-counter remedies, similar to conventional antihistamines. The literature shows numerous examples of trials and studies in which TCM has been used safely and effectively [32, 33].

Alternative/Integrative Medical Approaches in Sleep

Acupuncture and Sleep

A 2009 review of 30 studies showed 93% of the 30 qualifying studies demonstrated positive effects of acupuncture in improving aspects of sleep, including "reduced sleep latency, increased sleep and wake ratio (sleep efficiency), enhanced sleep duration and quality, and resolution of insomnia symptoms." Some employed objective measurements using wrist actigraphy or polysomnography with improved sleep-onset latency among patients with anxiety. Those that compared acupuncture with medications all showed the greater efficacy of acupuncture. Acupuncture, however, took longer to achieve benefits and more treatments to surpass the effectiveness of medication. Maintenance of acupuncture treatment effects were found to be up to 3.5 years at follow-up [34].

Acupuncture has known effects on various measures associated with the autonomic nervous system, including "blood pressure, pupil size, skin conductance, thermography recorded skin temperature, microneurography recorded muscle sympathetic nerve activities, heart rate and/or pulse rate, and heart rate variability." Basic scientific and clinical studies have indicated acupuncture regulates various neurotransmitters

and hormonal factors, including endorphins, serotonin, norepinephrine, adrenocorticotrophic hormone (ACTH), cortisol, acetylcholine (Ach), melatonin, substance P, other neuropeptides, gamma-aminobutyric acid (GABA), and nitric oxide, all of which play major roles in sleep regulation, higher cortical function, the hypothalamic pituitary adrenal axis, and the somatovisceral reflexes [35–37].

Research over many years has shown that administered by well-trained practitioners, acupuncture is exceptionally safe. A 2001 study published by the *British Medical Journal* encompassing a third of British acupuncturists and 34,000 treatments over 4 weeks showed no adverse events [38]. In 2011 an American Academy of Pediatrics survey of peer-reviewed literature concluded, "Our results support those from adult studies, which have found that acupuncture is safe when performed by appropriately trained practitioners" [39].

Other Alternative Medicine for Improving Sleep

Dietary sleep aids are common in everyday life, from a warm glass of milk to a cup of chamomile tea, which has been widely studied not only for its mild sedating effects but anti-inflammatory properties that may be used for conditions such as hemorrhoids [40]. The most studied medicines are melatonin and valerian, with limited research on acupuncture, acupressure, yoga, meditation, and Tai Chi [41]. However, a meta-analysis of four herbal monopreparations (valerian, chamomile, kava, and wuling) found no statistically significant difference between any herbal medicine and active control or placebo, for any of the 13 measures of efficacy [42].

Use of CAM for sleep is particularly widespread among older patients. Acupressure was found to have benefits for older patients in a meta-analysis encompassing 968 adult patients in 13 trials investigating the effects of TCM acupressure compared with standard and sham treatments [43].

The history of efficacy of herbal medicines for disordered sleep continues to be studied. A team from Guangzhou University has compiled a 20-year study of active ingredients including alkaloids, terpenoids, volatile oils, and flavonoids, insomnia experimental models and methods, results, and mechanisms. New compound prescriptions have been developed from single herbs with sedative-hypnotic effects. The pathways of TCM treatments range from perspectives such as regulating central neurotransmitters, influencing sleep-related cytokines, and improving central nervous system structure [44].

Conclusion

There has been a significant increase in the use of complementary and alternative medicine (CAM) in the United States, both in terms of public interest and practice. While drawing substantially on advances in the field of allergy/immunology for this review, there are additional vigorous research efforts on these and other sleep-compromising diseases, in Asia, Europe, and the United States. China, Korea, and India,

to name just three countries, have adopted stringent standards for proof of efficacy and safety. They are isolating active ingredients and exploring the mechanisms by which the medicines work. The Chinese formulary is a vast resource that has been used to treat universal maladies, including itching, sneezing, wheezing, and disordered sleep. By combining these ancient methods with the methods of modern science, effective and safe integrative practices can be developed to help patients.

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30 Assessment and Therapies for Sleep and Sleep-Related Breathing Disorders Associated with Atopic Disease in Children: A Dental Perspective

Kevin L. Boyd

In 1992 the American Academy of Pediatrics (AAP) published a policy statement on their concept of the *medical home* in an effort to assure that all infants, children, and adolescents ideally should have accessible, coordinated, continuous, comprehensive, compassionate, and family-centered care [1]. Among the services that were listed as being important for qualifying a healthcare facility as a *medical home* included, but were not limited to, provision of preventive care, growth and development assessments, appropriate screening, healthcare supervision, patient and parental counseling about health and psychosocial issues, identification of the need for subspecialty consultation and referrals, and knowing from whom and where the referrals can be obtained. Following the AAP's example, in 2002 the American Academy of Pediatric Dentistry (AAPD) published their own version of the medical home concept in a landmark paper, *The dental home: A primary care oral health concept* [2]. This paper described that the essential concept of dental care for children of all ages is best managed when there is an established relationship between a practitioner who is familiar with the child and the child's family, which should also be provided for pediatric dental patients by or before the age of 1 year. In fact, after the age of 2 or 3 years, dentists actually have greater frequency of patient encounters with children than do primary care medical providers [3]. This provides opportunity to discuss with parents/adult caregivers *traditional* (cavities, gum disease, etc.) and non-*traditional* oral health issues, such as how morphology of the craniofacial-respiratory complex (CFRC) (Fig. 30.1) can be comorbid with certain atopic disease phenotypes. Dentists might also discuss how atopy might be indicative of underlying breathing hygiene problems during wakefulness and sleep and/or predictive of possible future susceptibility to systemic issues associated with comorbid malocclusion (*maxilla-mandibular compromise*) and nasal disuse (chronic mouth breathing). They might also

K. L. Boyd (✉)
Dentistry for Children and Families, Chicago, IL, USA

Ann & Robert H. Lurie, Children's Hospital of Chicago, Chicago, IL, USA

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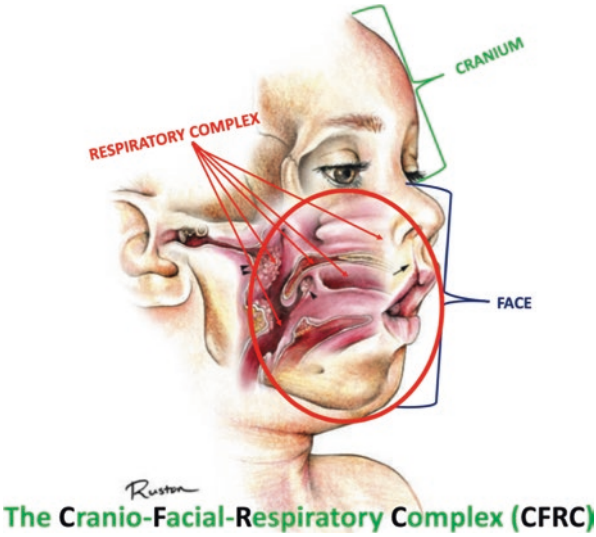


Fig. 30.1 The craniofacial-respiratory complex. (From Garg et al. [33], with permission)

consider making recommendations to seek further consultation from an appropriately trained and qualified healthcare professional, such as a pediatrician, otolaryngologist, allergist, orofacial myofunctional therapist or sleep medicine specialist.

Malocclusion as a Comorbidity of Atopic Disease

Human skeletal malocclusion (HSM), defined as the narrowing within the coronal plane, retracting within the sagittal plane, and lengthening of the horizontal plane of the mandible and maxilla (the maxillo-mandibular complex), with or without associated crowding and misalignment of teeth, is a condition that is prevalent in industrialized societies when compared to nonindustrialized cultures [4, 5]. This is usually first detectable before a child starts to shed their deciduous dentition (baby teeth), by approximately age 6–7 years. Some SM phenotypes known to be associated with atopic diseases of childhood [6, 7] can be diagnosed and appropriately intervened upon during school-age/preschool-age years. In addition to their known association with atopic diseases of childhood, pediatric SM correction, specifically with rapid maxillary expansion, is often associated with symptom mitigation of many non-atopic diseases as well, such as chronic otitis media, conductive hearing loss, and sleep-related breathing disorders (SRDB) [8]. Accordingly, it is important for dental and other healthcare professionals who provide services for children to be knowledgeable about screening for *all* types of SRDB comorbidities and risk factors, including not only physical(CFRC) and behavioral traits, but also pre-natal factors such as exposure to ethanol, first-/second- hand tobacco smoke and maternal (gestational) apnea.

HSM phenotypes most commonly associated with atopic diseases of childhood are unilateral posterior crossbite [7], higher gonial angles, shorter and retrusive

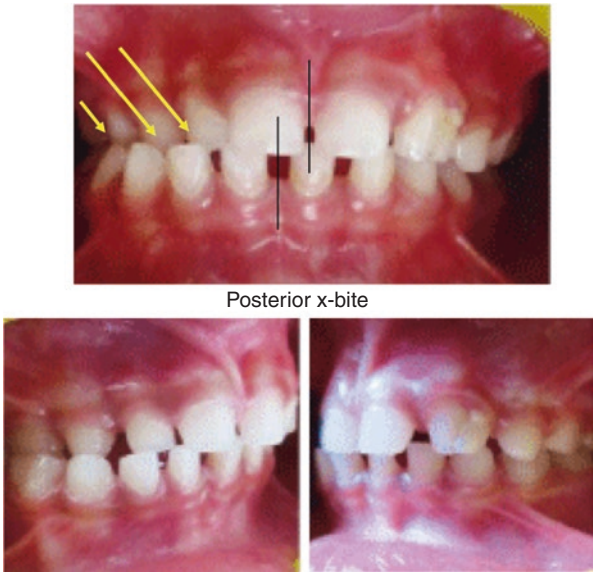


Fig. 30.2 Posterior x-bite

mandible and maxilla [9, 10], anterior open bite [11], vertical skeletal growth pattern (long face), higher palates, narrower maxillary molar widths, and excessive overjets and narrow pharyngeal airway space [6]. *Unilateral posterior crossbites* (Fig. 30.2) are characterized by an asymmetric shifting of a transversly constricted mandible (lower jaw) toward one particularly favored side of the opposing maxilla (upper jaw). They are usually first detectable in the primary dentition (baby teeth, under the age of 6). If left untreated after initial detection, they can precipitate to more serious skeletal involvement which can lead to noticeable facial asymmetries in adolescence and beyond. This in turn can lead to permanent mandibular asymmetry and structural changes within the temporomandibular joint (TMJ) complex [12]. Similarly, Class II SM which is most often characterized by mandibular retrognathia (Fig. 30.3) can also, albeit less frequently, involve coincident retrusion of the maxilla. Class III SM, most often characterized by maxillary retrognathia (Fig. 30.4), is usually first detectable during the earlier stages of dentofacial development (i.e, the deciduous and early mixed dentition). They are often left untreated until a child has shed most of their primary teeth somewhere between the age of 9 and 14, at which time most orthodontists recommend beginning orthodontic treatment (braces) [14]. We hypothesize this delay in SM diagnosis and timliness of intervention might result in a child becoming symptomatic from various atopic and non-atopic systemic health CNCD comorbidities, such as SDB/OSA, ADHD, and other CNCDs due to inadequate pharyngeal airway space and mouth breathing/nasal disuse. *Vertical skeletal growth* (Fig. 30.5) pattern (long face) is characterized by lengthening of the lower face as the mandible grows downward and away from the cranial base and, again, similar to posterior crossbites and Class II retrognathia,



Fig. 30.3 (**a**) Pre-Tx facial and profile and (**b**) progress Tx facial and profile. SM Class II profile



Fig. 30.4 HSM Class III profile

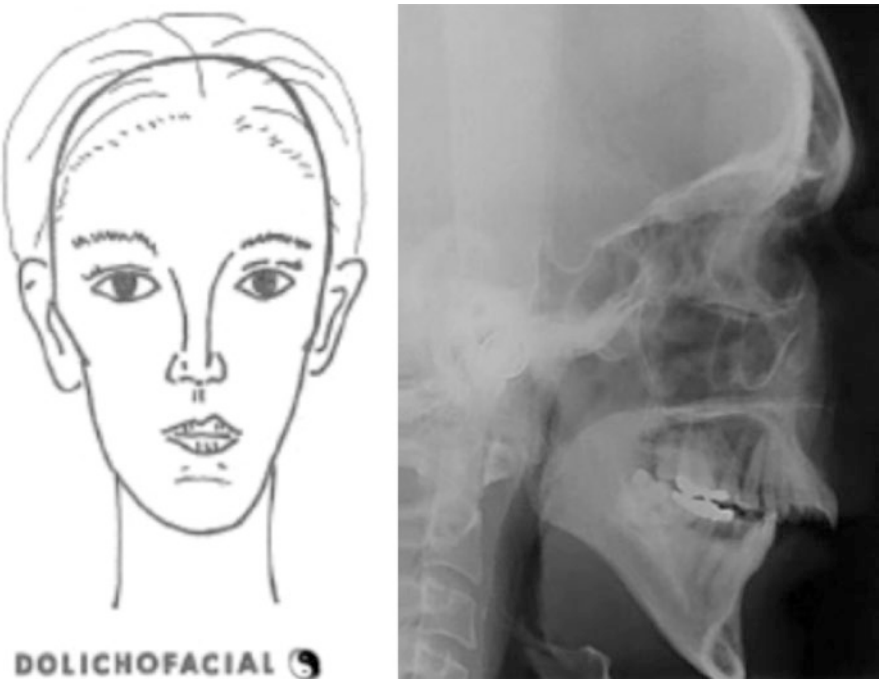


Fig. 30.5 Vertical facial growth (long-face phenotype)



Fig. 30.6 Anterior open bite

is often initially detectable and treatable in the primary dentition and early mixed dentition. It can worsen beyond if left unaddressed with effective intervention strategies [15]. *Anterior open bite* (Fig. 30.6), as the name implies, is characterized by an inability of the upper front teeth to close over the lower front teeth. This is in an effort to establish a normal overbite when the upper and lower posterior teeth (molars) are occluding with one another. Again, anterior open bites are often first detectable during early childhood but also can frequently appear initially at more mature phases of dentofacial development. Prevalence of specific SM phenotypes in the primary and early mixed dentition is approximately 20% and rises to 70% upon the initial eruption of the permanent teeth around age 7 [16]. Because of this, we believe SM and possible existing or future comorbidities, should be screened for at much younger ages than is now considered as being *conventional*.

Using Evolutionary Medicine to Approach Dentistry

The relatively recent appearance of chronic *Western diseases* in humans, such as allergeric rhinitis, obesity, type 2 diabetes, cardiovascular disease, dental caries (cavities), skeletal malocclusion, etc., is very likely *not* the result of Mendelian genetic change over the past few centuries. A more plausible explanation is in evaluating modern health problems from an evolutionary perspective. Evolutionary medicine (EM), also known as Darwinian medicine, provides a useful framework for understanding modern systemic diseases [17, 18]; evolutionary oral medicine, or Darwinian dentistry, is the branch of EM whose goals are to understand the evolutionary origins of oral diseases and to use this understanding for development of diagnostic, preventive, clinical treatment and research strategies. Similar to obesity, obstructive sleep apnea, and type 2 diabetes, *oral* diseases of

civilization (DCs) also seem to follow a predictable pattern of pathogenesis. Specifically, if a susceptible individual is identified early, oral DCs can often be *prevented*. Furthermore, if signs and symptoms are detected early, oral DCs can often be successfully *reversed* and/or *controlled/treated*. Finally, if not prevented, reversed, and/or appropriately *controlled/treated*, systemic, and/or oral DCs can threaten health, well-being, and survival. *Boyd* and Sheldon [19] give a detailed explanation for how a genomic-environmental *mismatch* hypothesis (18) helps explain the relatively sudden appearance of interrelated modern CNCD epidemics such as HSM and SDB/OSA that are seemingly coincident with the phenomenon of cultural industrialization. SM is most accurately described as an epigenetically modulated (genetic-environmental) disorder and appears correlated with cultural industrialization.

Comorbid Malocclusion and Naso-Respiratory Compromise: Which Comes First?

Mostly based upon the work of Harvold [20] in the early 1980s, it is often reported that the naso-respiratory compromise (nasal disuse, habitual mouth breathing) is *the* primary factor in the development of narrowed and lengthened jaws and faces of so-afflicted children; that is, so-called *adenoid facies* (aka, *allergic face*, *long-face syndrome*), and other malocclusion phenotypes commonly associated with atopy in childhood including: crossbites, crowded teeth, open bites, short mandibles, and/or maxillas and retrognathia, might indeed be exacerbated by ATH, but it has been hypothesized that ATH is not necessarily the primary intiating etiological factor. In a recently published essay on the controversy surrounding whether ATH usually preceedes lengthening and narrowing of jaws and faces, or vice-versa, Stupak and Park [8] cite Christian Guilleminault, the Stanford University pediatrician and Sleep Medicine physician who in 1976 first identified OSA as a pediatric disease [21], as also one of the first to suggest that malocclusion precipitates adenoid/tonsillar tissue hypertrophy-related breathing problems rather than vice versa [8]. Through multiple studies, Guilleminault teaches that facial structure and abnormal function, tone and/or equilibrium of the tongue, lips and facial expression, and masticatory musculature may be the inciting event triggering mouth breathing and the eventual hypertrophied adenotonsillar tissue. This line of thinking that malocclusion precipitates breathing problems rather than vice versa challenges conventional teaching. This implies that appropriately applied orthodontic/dentofacial orthopedic forces in the primary or early mixed dentition (i.e., before the age of 7) can improve maladapted bony structures of the craniofacial and respiratory complexes. Additional intervention with orofacial myofunctional therapy [22], surgical revision/release of soft tissue restrictions such as ankyloglossia (tongue-tie) [23], and efforts to restore optimal naso-respiratory function, such as Buteyko therapy [24], might also help mitigate the symptoms of naso-respiratory resistance, nasal disuse, and habitual mouth breathing that are commonly associated with atopic and nonatopic disease in childhood. Further research in this area is needed.

Orthodontic/Dentofacial Orthopedic (O/DO) Strategies in Early Childhood

As previously stated, short retrusive mandibles (Class II SM) and maxillas (Class III SM), unilateral posterior crossbites, vertical skeletal growth, anterior open bites, and other SM phenotypes (e.g., highly vaulted hard palates, crowded teeth, obtuse nose-lip angles, etc.) are often comorbid with atopy and other non-atopic health conditions (e.g., preterm birth, intrauterine growth restriction, obesity, fetal exposure to alcohol and/or primary/secondary tobacco smoke, deviated nasal septum, etc.). Most, if not all of the aforementioned co-morbidities are usually first evident in the primary/early mixed dentition, and usually worsen in later childhood and adolescence without appropriate intervention are often comorbid with naso-respiratory compromise and associated neurological, somatic, and metabolic problems associated with nasal disuse, habitual mouth breathing, and intermittent hypoxia during wakefulness and sleep. If not adequately controlled or left untreated, it seems reasonable to suggest that delaying orthodontic intervention until adolescence/pre-adolescence might pose unnecessary health risk for such identified at-risk children. Furthermore, as published evidence suggests, appropriately timed and applied orthodontic/dentofacial orthopedic intervention treatment strategies can often yield the therapeutic benefit of decreased naso-respiratory resistance and conversion from a habitual oral to a habitual nasal mode of respiration [25–27].

Class II HSM (also called distoclusion in the orthodontic peer-reviewed literature since the mid-/late nineteenth century) when initially observed in preschool-/school-age years does not self-correct [28] and tends to worsen [13]. When therapeutic O/DO intervention strategies are implemented, they can indeed resolve Class II and Class III HSM phenotypes. We hypothesize they might also improve naso-respiratory competence.

Non-retractive O/DO Intervention Strategies

Maxillary insufficiency, defined by both constriction in the transverse (width) dimension and retrusion in the sagittal (length) dimension, also called maxillary sagittal insufficiency, is the skeletal phenotype that is most commonly associated with SM Class III. However, McNamara demonstrated that retrusion of the upper jaw and midface can also be strongly associated with distoclusion/HSM Class II [13]. Maxillary expansion as an adjunctive therapeutic intervention for recurrent OSA symptoms adjacent to surgical removal of hypertrophied adenoid tissue was early described in a 1918 article published in the *Boston Medical Journal* [29]: “It would be entirely useless to hope for permanent relief by removing the nasal obstruction if the jaws did not first receive proper orthodontic treatment. It is important to undertake this at an early age, the principal aim being not only to straighten the teeth, but to stimulate growth of the bones of the entire face.” Maxillary and mandibular protraction are both known to improve naso-respiratory competence in children with comorbid retrusive HSM phenotypes, of either or both jaws, and

naso-respiratory compromise. To date, there is not yet an accepted diagnostic descriptive classification for the HSM phenotype that is characterized by maxillo-mandibular skeletal retrusion (MMR).

MMR is a primary preoperative diagnostic indication for maxilla-mandibular advancement (MMA) orthognathic surgery in nongrowing (adult) patients with unresolved OSA. Further works might explore precisely when, in an adult patient's earlier life, did an MMR phenotype initially become evident.

Maxillary and Mandibular Retrusion Phenotypes as SRBD Comorbidities

In 1992 McNamara demonstrated that in Class III "occlusal (retrusion of the maxillary first permanent molar relationship)-skeletal" (retrusion of the entire maxillary base) in 6-year-old (± 9 months) subjects, nonsurgical protraction of the entire maxillary complex with a reverse traction face mask appliance, in combination with transverse expansion of the maxilla utilizing a rapid palatal expansion appliance (Fig. 30.7), resulted in advancement and counterclockwise rotation of the entire maxillofacial complex [30]. This is in much the same manner as surgical MMA in adult patents. A retrospective analysis of 277 cephalometric lateral head films in untreated Class II "occlusal-skeletal" in 8–10-year-olds showed that many Class II subjects are *not* maxillary *protrusive*, but rather, most are actually maxillary neutral or *retrusive* [13]. As evaluation of skeletal traits associated with the diagnoses of

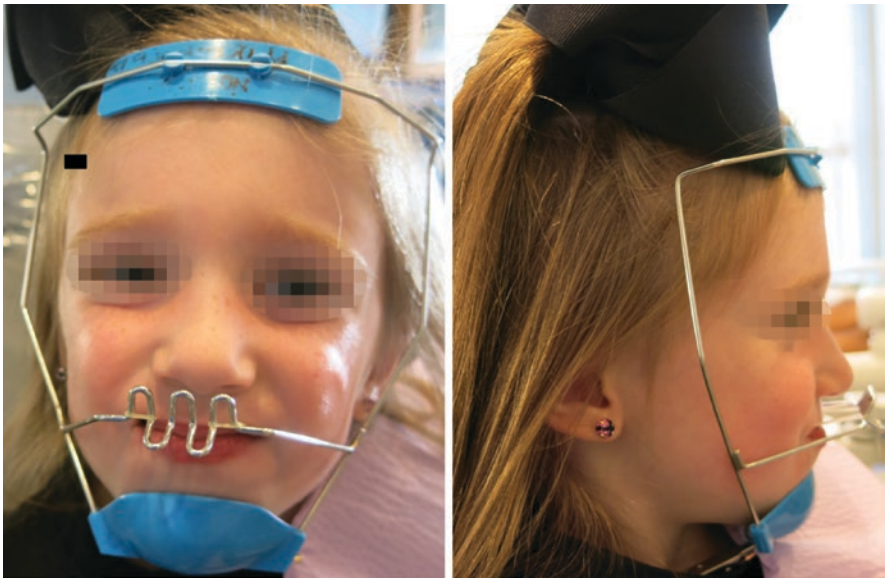


Fig. 30.7 Reverse pull face mask

Class II and Class III malocclusion has been the primary protocol objective, pre-/posttreatment effect data concerning airway health parameters has not been assessed.

As the mandibular retrognathia commonly associated with Class II HSM may also often be a diagnostic facial feature of SRBD, and that maxillary retrognathia commonly associated with Class III *and* Class II HSM may also be a comorbidity of SRBD, it is plausible to suggest that resolving the structural trait maldevelopments associated with both HSM types could lead to functional improvements such as improved airway competence [19, 31].

In 1976 Hershey [27] showed that rapid maxillary expansion is not only an effective method for increasing the width of narrow maxillary arches, but also reduces nasal resistance from levels associated with mouth breathing to levels compatible with normal nasal respiration. In 1980 both Subtelny [31] and Oktay [25] showed that with the addition of a reverse pull face mask, traction appliance to a maxillary retrusive patient undergoing rapid palatal expansion could increase the posterior pharyngeal airway space at the level of the naso- and upper oropharynx. Similarly, many other functional orthopedic appliance treatment strategies that are designed to protract retrusive mandibles, such as Twin Block, Herbst, Bionator, Biobloc [19], etc., also have the added benefit of increasing the posterior airway space at the level of the oro- and hypopharynx.

Conclusion

Many growing children afflicted with atopic diseases have comorbid structural maldevelopments of the craniofacial-respiratory complex (CFRC). Although the epidemiology is not well characterized, several characteristic patterns of human skeletal malocclusion in atopic patients have been noted: constricted width of the maxilla (unilateral posterior crossbites), excessive vertical jaw growth (long face), anterior open bites, and decreased length (short) of mandibles and maxillas. These particular HSM traits represent dysmorphology in all three planes of the CFRC space and are all associated with habitual mouth breathing/nasal disuse. As many HSM phenotypes are first identifiable in early childhood, we believe that in the presence of respiratory dysfunction, treatment for HSM should be discussed at much earlier ages than is currently considered common practice (i.e., before the age of 7).

Providing assurances of cavity-free teeth, disease-free gums, healthy TMJ/jaw joints, and uncrowded straight-toothed smiles, have all rightfully long been the primary criteria for defining optimal pediatric oral health and orthodontic treatment success. With the recent "rediscovery" from within past medical and dental literature dating back to the nineteenth and early 20th centuries [32, 34–39] that HSM, naso-respiratory competence, and neurological health are all interrelated, it has become increasingly apparent that the *current* list of criteria necessary for defining optimal oral health and orthodontic success should be expanded to include the optimizing the ability to breathe habitually through the nose during wakefulness and sleep, at the earliest stage of a child's CFRC development as might be feasible.

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Surgical Management of Allergic Disease to Treat Sleep Disturbance in Children and Adults

31

Matthew Purkey, Chris Gouveia, and Bruce Tan

Sleep is an essential physiologic function that contributes to quality of life [1], childhood development and learning [2], immune function [3], and healing [4]. Allergic disease has a well-established role in the quality of sleep for children and adults [5]. This relationship is complex and multifactorial, and is due in great part to exacerbation of allergic symptoms at night due to circadian fluctuations of cortisol, histamine, and cytokines levels [6, 7].

First-line therapy for allergic conditions includes medical treatments such as topical intranasal sprays, systemic medications including antihistamines and steroids, and immunotherapy. Initial management of sleep disorders related to allergy, besides treatment of the underlying condition, includes lifestyle/sleep hygiene modifications, dental appliances, and positive airway pressure [8]. When disease is refractory to medical therapy, surgery can play a role in management. While no procedure specifically aims to cure allergic disease, surgery can address the sequelae that contribute to decreased sleep quality. This chapter aims to discuss the effects of surgical management on allergy-associated conditions in which sleep disturbance is prominent.

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA), diagnosed on polysomnography (PSG) and clinical evaluation, is characterized by the occurrence of repeated respiratory events (including apneas, hypopneas, and respiratory effort-related arousals (RERAs)) with concurrent symptoms of OSA such as loud snoring, excessive daytime fatigue, and non-restorative sleep [9]. In children, a spectrum of disorders ranging from partial

M. Purkey (✉) · C. Gouveia · B. Tan
Department of Otolaryngology, Head & Neck Surgery, Northwestern Memorial Hospital, Chicago, IL, USA
e-mail: matthew.purkey@northwestern.edu

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obstruction and snoring to apnea is contained within the pediatric sleep-disordered breathing (SDB) spectrum. Besides the symptoms listed above, SDB can manifest as difficulty in school or acting out in children [10]. OSA not only affects quality of life but has also been associated with increased rates of cardiovascular disease, insulin resistance, and mortality [11–13]. There is a well-described connection between allergic disease and OSA, particularly asthma and allergic rhinitis [14–16]. The two entities influence one another in a deleterious and synergistic fashion. For example, the prevalence of snoring and apneic events as well as overall symptom burden is significantly worse in patients with comorbid asthma [17], while patients with poorly controlled or difficult-to-control asthma have comorbid OSA at a rate of almost 90% [18]. A number of pathophysiologic relationships linking allergic disease and OSA have been proposed. One model suggests that systemic inflammation can weaken the dilator muscles of the upper airway while also activating neural responses that override mechanisms in place to protect upper airway patency [6]. Systemic or local steroids can also result in the deposition or redistribution of fat in the airway [19]. Finally, increased negative inspiratory pressure and exaggerated contraction of the respiratory musculature seen in asthma attacks promote pharyngeal remodeling and collapse [17].

Surgical interventions for OSA are targeted at relieving sites of anatomic obstruction and dynamic collapse (Fig. 31.1). The lymphoid tissues of Waldeyer's ring are the most common site of obstruction in pediatric populations, though hypertrophy

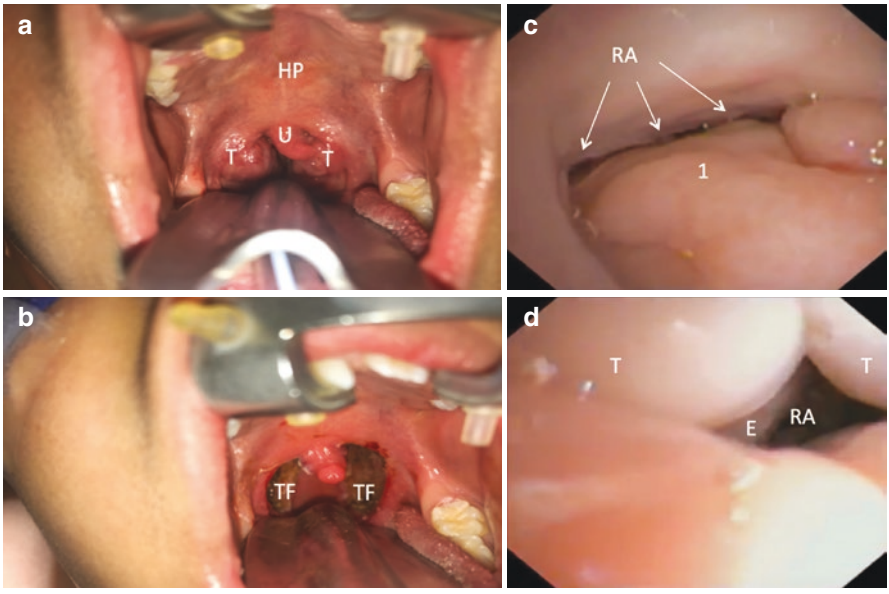


Fig. 31.1 Adenotonsillar obstruction. Pre- (**a**) and postoperative (**b**) direct view of a pediatric patient with significant hypertrophy of the tonsils and adenoids. Endoscopic view of airway obstruction by the adenoids (**c**) and tonsils (**d**). *T* palatine tonsil, *U* uvula, *HP* hard palate, *TF* tonsillar fossa, *A* adenoidal tissue, *E* epiglottis, *RA* residual airway

of these structures alone has not been shown to directly cause sleep apnea [20]. Additional contributors to SDB include upper airway tone disorders, craniofacial abnormalities, inflammation, or genetic predisposition [21]. SDB is most common between ages 2 and 6, which is also the time when the tonsillar tissues occupy the largest percentage of the airway [20]. Subsequently, one of the most common procedures performed in patients with OSA, particularly in children, is (palatine) tonsillectomy ± adenoidectomy.

Preoperative Evaluation

Each of the procedures described in this chapter is routinely performed under general anesthesia (GA), and as such, preoperative patient evaluation must include assessment of candidacy for the risks of GA. This evaluation should ideally take place within 30 days of surgery and include a thorough history and physical, imaging, or lab tests as indicated, an assessment of performance status (typically measured in metabolic equivalents or METs), and a careful assessment of risks vs. benefits of the planned operation. Additionally, in pediatric patients, it is important to assess the ability of the parents/guardians to support and care for the child after surgery. As noted above, patients with OSA are at higher risk for several comorbidities. Special attention should be paid to the cardiac and respiratory systems in these patients.

Procedure

Both extracapsular and intracapsular tonsillectomy (or tonsillotomy) techniques are commonly used today for management of OSA. The overall goal of the surgery is to sufficiently debulk the tonsillar tissue to relieve obstruction and prevent regrowth. Both methods utilize a transoral approach under general anesthesia. In the extracapsular approach, the tonsil is separated from fibrous attachments to the pharyngeal sidewalls with intervening blood vessels cauterized using a variety of techniques. In the intracapsular variation of the procedure, tonsillar tissue is removed using a microdebrider, while the tonsillar capsule is left in place to act as a biologic dressing. While intracapsular tonsillectomy is associated with higher rates of regrowth, some authors argue in favor of this approach as it has been shown to reduce postoperative pain and hemorrhage rates and hasten return to school/work while achieving similar sleep outcomes in both children and adults [22, 23]. The adenoids can be removed via several methods, including cold dissection, cauterization, coblation, and microdebridement. Otherwise healthy adult patients are typically discharged home on the day of surgery unless they have complex comorbidities or severe sleep apnea. Pediatric patients are routinely observed overnight if there are concerns regarding severity of OSA, ability to return to the hospital if complications were to occur, or ability to tolerate PO (especially in patients with Downs syndrome or other intellectual disabilities) [24].

Recovery

Postsurgical pain after adenotonsillectomy can be significant in adults. Patients frequently require at least 1 week off of school or work. We counsel our patients to expect up to 2 weeks of moderate to severe throat pain, referred otalgia, halitosis, and abnormal appearance of the oropharynx. We also routinely advise patients to follow a mechanical soft diet for 2 weeks after surgery, both for comfort and also to avoid direct trauma from sharp foods to the pharynx that could cause hemorrhage.

Complications

The most common complication of tonsillectomy is postoperative hemorrhage, which occurs in up to 5% of cases depending on patient risk factors and surgical instrument [25]. Primary hemorrhage occurs within 24 h of surgery and is related to surgical technique, while secondary hemorrhage can occur up to 10–14 days post-op and is classically associated with sloughing or loss of hemostatic eschar in the tonsillar beds. While usually easily controllable with conservative measures or return to OR, quick recognition and control is critical as untreated hemorrhage can result in significant blood loss and airway compromise. Other complications include respiratory depression (for this reason, narcotic pain medications are selectively prescribed), dehydration from poor PO tolerance (occasionally requiring admission for IV hydration), and rarely pulmonary edema resulting from sudden relief of chronic upper airway obstruction. With adenoidectomy, there is a risk of postoperative velopharyngeal insufficiency (VPI). VPI is characterized by hypernasal speech and results when over-resection of the adenoids prevents complete nasopharyngeal inlet closure [26].

Outcomes

While no randomized trials exist, the majority of studies on sleep outcomes after adenotonsillectomy in children suggests significant improvement in symptoms after surgery [27]. Cure rates range widely in the literature. A recent meta-analysis which included studies defining cure as post-op AHI of <1–5 events/h demonstrated a cure rate of 66% (60% when limited to studies with an AHI < 1) [28]. A similar meta-analysis of tonsillectomy for SDB in adults found improvements after surgery in AHI (average 65% reduction, mean difference − 30.2/h), oxygen nadir, and EPSS score, with a 85% success rate (defined as posttreatment AHI < 20 and overall decrease >50%) and a cure rate of 57% for all comers and 84% for patients with an AHI <30 [29]. Predictors of failure to cure include older age, obesity, severe disease, craniofacial abnormalities, and presence of asthma [30, 31]. A more recent prospective study by Smith et al. demonstrated a significant improvement in several well-validated OSA measures [32].

While tonsillectomy can be a successful sole treatment modality in adults, the lymphoid tissue in Waldeyer's ring shrinks significantly in adulthood, and thus, tonsillar hypertrophy has less contribution to OSA in most adults. For this reason, a number of surgical interventions have been developed and are available to the sleep surgeon to address other sites of obstruction. Determination of the main levels of obstruction is the first step, which can be accomplished with in-office flexible laryngoscopy and/or operative sleep endoscopy. Obstruction can be classified by anatomic region into nasal (covered later), retropalatal, or retroglossal categories. Isolated retroglossal obstruction (i.e., lingual tonsils, base of tongue, epiglottis) is more prevalent than retropalatal obstruction in the literature, but as high as 76% of patients have multilevel obstruction [33, 34].

Palatal obstruction is frequently addressed with uvulopalatopharyngoplasty (UPPP), a procedure that includes tonsillectomy, uvulectomy, and widening of the oropharyngeal airway via pharyngoplasty. Like in adenoidectomy, VPI is a potential side effect of UPPP occurring at a rate of 8% in a recent meta-analysis [35]. Other sleep procedures include genioglossus advancement, hyoid suspension, and maxillomandibular advancement (MMA). The Stanford Protocol is a well-known stepwise approach to surgical OSA treatment. Phase I includes UPPP ± genioglossus advancement ± hyoid suspension and was successful in 71–78% of mild/moderate OSA patients and 42% of severe OSA patients in the original study [36]. Phase II, MMA, was successful in 100% of patients [36]. Finally, hypoglossal nerve stimulator implantation is a newer technology that aims to augment tone of the pharyngeal dilators during sleep. In early studies, the devices have shown promise in reducing AHI and improving quality-of-life measures [37, 38].

Allergic Rhinitis

The relationship between allergic rhinitis (AR) and sleep disturbance has been well documented in the literature [39–41]. Patients with nasal obstruction secondary to allergic rhinitis were 1.8× more likely to have OSA in the Wisconsin sleep cohort study (a prospective population-based study of 1522 patients started in 1988) [42]. In children, AR is a risk factor for snoring. There is a significant increase in the prevalence and frequency of snoring in children with AR compared to non-AR controls, with up to 60% of children with AR exhibiting symptoms [40]. Even when not associated with clinical SBD or OSA, there are significant quality-of-life disturbances including daytime sleepiness and morning headaches among AR patients. Further, even when OSA was controlled medically, patients with AR had a 3× higher rate of snoring [43].

AR causes sleep disruption via several complex and interactive mechanisms. The disease process itself results in upper airway resistance which leads to obstructive events and elevated work of breathing. Additionally, poor symptomatic control produces sleep-onset and maintenance issues, while some commonly prescribed medications can also contribute to sleeplessness [44].

The most common complaint of patients with AR, and that which can be targeted by surgical interventions, is nasal obstruction [45]. The nasal airway accounts for two-thirds of total airway resistance, so it is easy to see why nasal obstruction diminishes sleep quality [46]. Within the nasal airway, the area of highest resistance is the narrowest portion known as the internal nasal valve. This "valve" is bounded by the floor of the nose inferiorly, the nasal septum medially, the upper lateral cartilage superiorly, and the head of the inferior turbinate laterally. The turbinates are fingerlike projections on the lateral nasal wall that consist of the bone with overlying mucoperiosteum. Most individuals have three turbinates on each side, with a small percentage (~20%) having a fourth "supreme" turbinate. They function to direct air posteriorly in a laminar fashion toward the nasopharynx as well as to increase the internal surface area of the nose and aid in warming and humidification of inhaled air. The inferior turbinates contain erectile tissue that physiologically enlarges in alternate fashion in a phenomenon known as the nasal cycle. Enlargement of the turbinates, particularly the inferior turbinate, is frequently observed in allergic rhinitis but can also be seen in vasomotor rhinitis, non-allergic rhinitis with eosinophilia, and rhinitis medicamentosa (rebound congestion after over-usage of decongestant sprays such as oxymetazoline). In contrast, the nasal septum is a midline structure composed of the quadrangular cartilage and bony contributions from the maxillary bone, the ethmoid bone, the palatine bone, and the vomer, with an overlying mucoperichondrial layer. Deviations of the septum can occur in any of the cartilaginous or osseous components and are frequently congenital or developmental but can also be acquired after severe nasal trauma (Fig. 31.2).

Enlarged inferior turbinates, anatomical middle turbinate variants like a concha bullosa, or significantly deviated septums can have a significant impact on breathing during sleep and are a frequent offender in nasal obstruction. The

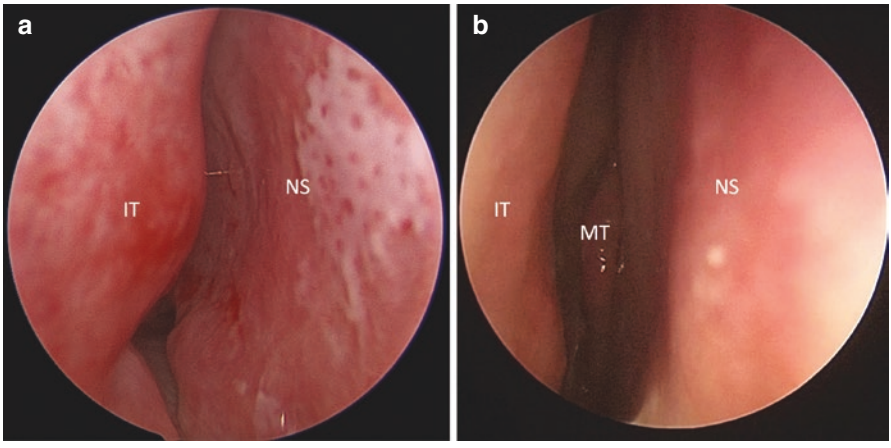


Fig. 31.2 Nasal obstruction in allergic disease. Endoscopic view of the right nasal vestibule in (**a**) patient with severe septal deviation with near-complete occlusion of the right nasal passage and squamous metaplasia of the septum; (**b**) 3 months after a septoplasty and submucosal inferior turbinate resection. *IT* inferior turbinate, *MT* middle turbinate, *NS* nasal septum

inferior turbinates predictably enlarge at night due to both the dependent position of the sleeper and an inflammatory circadian rhythm that worsens throughout the night . Chronic obstruction also dampens nasal receptor reflexes, which normally dilate the nasal passages during sleep [47]. Further, the requisite oral breathing during sleep results in tongue base obstruction from inferior displacement of the mandible as well as altered pharyngeal musculature [48]. While AR is rarely a surgically treated condition, surgical treatment of AR focuses on turbinate reduction but should also address any other sites of nasal cavity obstruction, including deviation of the nasal septum.

Preoperative Evaluation

In-office evaluation begins with direct and endoscopic visualization of the turbinates at baseline and then after application of topical decongestant. The exam is also important to evaluate for alternate sources of obstructive pathology like septal deviation, sinusitis, nasal polyps, adenoid hypertrophy, or obstructive neoplasia. A significant decrease in the size of the turbinates with concomitant improvement in symptoms after application of oxymetazoline or other α-agonists suggests the patient may benefit from surgical reduction. If endoscopy is unavailable, a lateral x-ray may reveal adenoid hypertrophy, and CT of the sinuses may adequately evaluate for the presence of sinusitis, nasal lesions, or septal deviation as a source of obstruction.

Procedure

Inferior turbinate reduction can be accomplished via several techniques with the shared purpose of reducing the overall bulk of the tissue. This is often accomplished in the OR under sedation, but in select patients, the procedure can be performed under local anesthesia in the office. Using direct visualization or a 0-degree rigid endoscope, a stab incision is made into the head of the turbinate. An elevating instrument is used to raise a soft tissue flap off of the underlying bone. Finally, redundant soft tissue is removed until adequate reduction of the turbinate is achieved. In an awake patient, an ablative instrument is directly inserted submucosally and activated to achieve shrinking of the turbinate.

Septoplasty begins with a vertical incision through columellar skin and nasal mucosa down to the cartilaginous septum. Once within the avascular submucoperichondrial plane, a soft tissue flap is raised posteriorly to include all deviated portions of the cartilaginous and bony septum. An incision is then made through the anterior cartilage, and an opposing flap is raised on the contralateral side of the septum. With care to leave an adequate amount of dorsal and caudal cartilage in place for nose support, additional cuts are made to form a rectangular portion of cartilage that is removed with a grasping instrument. If any bony spurs or deviations exist, these are also removed. The incision is closed and splints may be placed for 1 week.

Recovery

Both turbinate reduction and septoplasty are generally well-tolerated. We counsel our patients that symptoms of nasal obstruction may worsen due to edema in the immediate postoperative period, especially if septal splints are placed. OSA patients should also be advised that they may not be able to use (or may not gain benefit) from nasal delivery systems at first. If this is the case and the OSA is severe, we will occasionally admit patients overnight for respiratory monitoring. Saline rinses are typically started on postoperative day 1 to prevent crusting. Septal splints are removed on postoperative day 7.

Complications

Complications of septoplasty and turbinate reduction are uncommon. A septal hematoma can form if persistent intraseptal bleeding occurs. Inadvertent flap tears or planned mucosal incisions help prevent this complication, which presents as severe intranasal pain in the postoperative period. Incision and drainage relieves the pressure, prevents reaccumulation, and lowers risk for chondronecrosis and saddle nose deformity. Excessive resection of the quadrangular cartilage struts can also result in saddle nose deformity. If septal flap tears occur on contralateral sides communicate, patients can develop a whistling sensation as air flows turbulently toward the nasopharynx through the perforation. Placement of a septal button or enlargement of the perforation typically alleviate this symptom. The intranasal splints left postoperatively have rarely been associated with toxic shock syndrome [49]. Prophylactic antibiotics have not been shown to prevent this complication [50]. Overaggressive resection of the perpendicular plate of the ethmoid bone can result in a cerebrospinal fluid (CSF) leak. A controversial complication of turbinate reduction is “empty nose syndrome” or atrophic rhinitis, which is the sensation of diminished airflow and an increase in intranasal crusting [51].

Outcomes

Numerous studies have demonstrated improvement in sleep outcomes after surgery for nasal obstruction. Studies by Schuaib et al. and Moxness and Nordgard both demonstrated significant AHI reductions after septoplasty and turbinate reduction [52]. A more recent meta-analysis of 320 patients found significant improvement in RDI and Epworth Sleepiness Scale scores after nasal surgery, though notably did not find a significant improvement in AHI [53].

Aside from direct results related to opening of the nasal obstruction, nasal obstruction surgery has been shown to improve compliance with positive airway pressure delivery devices. A systematic review by Camacho et al. showed an improvement in regular CPAP use from 38.7% pre-surgery to 90.2% after surgery. The mean use increased from 3.0 h/night to 5.5 h/night in the same review [54].

Chronic Sinusitis

Chronic sinusitis (CRS) is a prevalent condition estimated to affect as many as 7–17% of adults that is diagnosed based on symptoms and objective criteria [55]. Patients must have a combination of symptoms ("major" symptoms include facial pressure, hyposmia/anosmia, postnasal drip, and anterior rhinorrhea) for a minimum of 12 weeks plus evidence of sinusitis on imaging or direct visualization. CRS is also commonly encountered in children, though the exact prevalence is difficult to determine. Initial workup of pediatric patients should include consideration for underlying comorbid conditions such as cystic fibrosis or primary ciliary dyskinesia. Careful attention should be paid to the adenoids, as adenoidectomy is successful at alleviating CRS symptoms in 50% of children [56].

CRS has significant detrimental effects on quality of life, with impairments in general health domains particularly noted in sleep quality and fatigue [57]. Sleep dysfunction is much more prevalent in patients with CRS (up to 75%) compared to the general population [58]. The etiology of poor sleep in CRS patients is multifactorial. Like in AR, CRS (especially during an active infection) produces nasal obstruction – especially when nasal polyposis is present (Fig. 31.3) [59]. However,

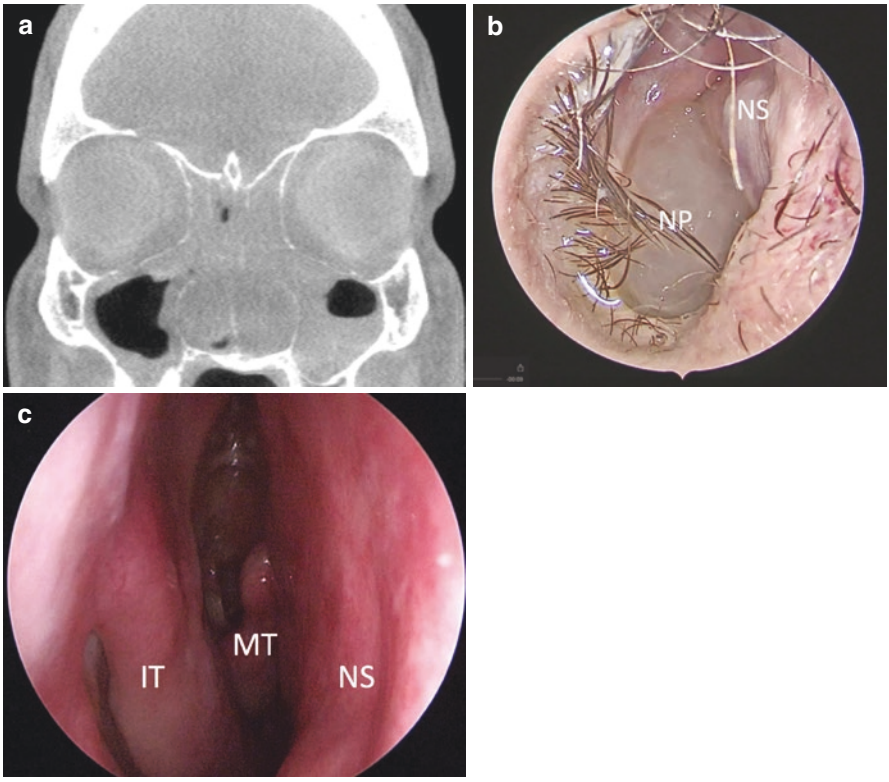


Fig. 31.3 Pre- and post-op endoscopic sinus surgery. (**a**) Coronal CT image of a patient with severe bilateral CRSwNP and (**b**) corresponding right-sided endoscopic image, as well as (**c**) 6 months after endoscopic sinus surgery. *NP* nasal polyp, *IT* inferior turbinate, *MT* middle turbinate, *NS* nasal septum

recent data suggests that obstruction alone does not account for the poor sleep quality seen in CRS patients. Other proposed etiologies for sleep quality impairment include the chronic state of inflammation, chronic pain, and depression [58, 60].

Evaluation

Preoperative diagnosis of CRS requires direct nasal endoscopy or a CT scan with appropriate findings of pus or polyps in the middle meatus or radiographic evidence of inflammation in the paranasal sinuses. Treatment of CRS begins with medical therapies. Topical intranasal sprays, oral steroids, and antibiotics are the cornerstones of treatment. If patients have refractory disease after an extended medical trial, surgery can play a role.

Procedure

The ultimate goal of surgery (known as functional endoscopic sinus surgery or FESS) is to enlarge the natural ostia of the maxillary, ethmoid, sphenoid, and frontal sinuses into the nasal cavity in order to improve drainage and facilitate delivery of topical medications directly to the sinus mucosa using a variety of rigid endoscopes and instruments. The procedure is frequently performed using image guidance via tracking probes on the instruments coupled to the CT scan. If septoplasty is necessary, this is performed first to allow better access to the lateral nasal structures. The uncinate process, a bony prominence on the lateral nasal wall in the area of the osteomeatal complex, is removed first to allow better visualization of the maxillary os. A combination of cutting instruments and debridement is then used to enlarge the maxillary antrostomy. Next, beginning with the ethmoid bulla cell, the ethmoid sinuses are opened and bony partitions taken down in an anterior to posterior fashion until the sphenoid os is reached, which is then enlarged. Removal of ethmoid cells is then carried forward in a posterior to anterior fashion along the skull base. Finally, the frontal sinus drainage system is addressed. Frontal procedures (Draf classification) range from clearing the superior uncinate process and anterior-most ethmoid cells to drilling of the floor of the frontal sinus depending on severity of disease. The same procedure is then repeated on the contralateral nasal cavity. Patients are discharged home on the day of surgery.

Balloon sinuplasty involves insertion of a small balloon catheter into the os of the sinuses and inflating it, theoretically dilating the opening similar to the goals of endoscopic sinus surgery and affording a less invasive surgical approach. Most practitioners advocate a conservative approach to FESS in children. A limited surgery ("mini-FESS") that includes a maxillary antrostomy, anterior ethmoidectomy, and removal of any polyps or other obvious obstructions is performed.

Recovery

FESS is generally well-tolerated. Patients are instructed to start saline rinses on postoperative day 1. Those that adhere closely to postoperative rinses have less symptoms and require less debridements [61]. Some patients with severe inflammatory disease may benefit from postoperative steroid rinses. Similarly, patients with signs of active infection can benefit from postoperative antibiotic courses. Neither steroid rinses nor antibiotics are required in all patients. Typically, three postoperative debridements are performed in the office to aid in healing.

Complication

The most serious complications of FESS involve damage to structures in the vicinity of the nasal cavity, namely, the orbit and skull base. While both complications occur in <1% of operations, the high volume of sinus surgery being performed today requires that the surgeon be familiar with recognizing and treating each [62].

Violation of the skull base results in a defect and CSF leak, which can lead to potentially devastating results including meningitis or intracranial abscess. Prophylactic antibiotics have not been shown to be beneficial and are not routinely given except in extenuating circumstances such as active sinus infection [63]. CSF leak can be recognized intraoperatively as flowing clear fluid or by visualization of pulsating dura/brain tissue. Postoperatively, CSF leak presents as clear, salty rhinorrhea often associated with pneumocephalus and headache. ß2 transferrin or intrathecal fluorescein tests can be used to aide in diagnosis, as can CT, MR, and CT cisternography. After identification and exposure of the defect, a number of techniques and materials are available to the surgeon. The overall goal is to successfully patch the leak using a combination of autologous and synthetic materials. Post-op adjuvant efforts aim to reduce intracranial pressure via avoidance of straining, heavy lifting, sneezing, etc.

While uncommon, a number of orbital complications can occur after FESS. If the medial orbital wall (or lamina papyracea) is violated, direct damage can be inflicted on the orbital contents, especially with overaggressive use of the microdebrider. Postoperative abscess can occur requiring ophthalmologic evaluation, antibiotics, and occasionally decompression. Emphysema can result if there is a defect in the lamina papyracea and the patient forces air intraorbitally by sneezing or blowing their nose. In rare instances the air can compress the retinal artery and cause vision loss, beginning with loss of the color red [63]. Direct damage to the optic nerve, which can sometimes be dehiscent in the sphenoid sinus, can also lead to vision loss. Finally, retrobulbar hematoma can occur if a vessel is transected intranasally and retracts intraorbitally. The most common culprit is the anterior ethmoid artery, a branch of the ophthalmic artery. Emergent decompression via lateral canthotomy and cantholysis must be performed to avoid loss of vision in the affected eye.

Table 31.1 Sleep outcomes after endoscopic sinus surgery

Author, year	Study type	*N*	Outcomes
Tosun (2009) [68]	Prospective cohort	27	Improved snoring and daytime sleepiness after surgery, no difference in AHI
Benninger (2010) [69]	Retrospective cohort	113	Improved sleep domain scores on RSDI after surgery
Alt (2014) [66]	Prospective cohort	219	Improved global and subdomain PSQI scores after surgery
DeConde (2014) [70]	Prospective cohort	363	Improved sleep domain scores on SNOT-22 questionnaire in surgical group (0.818 effect size)
Yalamanchali (2014) [71]	Retrospective cohort	56	Improvements in AHI for patients with moderate and severe OSA after surgery (though not curative)
Rottenberg (2015) [65]	Retrospective cohort	53	Improved Epworth sleepiness scale and PSQI scores after surgery

Outcomes

Several case series have demonstrated an improvement in sleep quality using objective measures after endoscopic sinus surgery as measured by PSQI and SNOT-22 scores (Table 31.1) [64–66]. In a large series with 187 patients, Alt et al. showed an improvement in PSQI scores in patients undergoing sinus surgery as compared to patients treated with medical therapy alone [67]. While the mechanism behind the improvement after surgery is incompletely understood, early results have shown promising results in regard to sleep outcomes after surgery. The efficacy of balloon sinuplasty is more controversial, as results have been at best mixed in the literature. It can be a good option for patients that are not otherwise surgical candidates. No studies have yet directly addressed sleep outcomes after balloon sinuplasty.

Conclusion

Allergic disease is frequently comorbid with a variety of conditions which have profound and well-documented effects on sleep quality via anatomic and physiologic mechanisms. When medical therapies fail to adequately alleviate symptoms, surgery can play a role in improving sleep outcomes.

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Appendix: Food Allergy and Sleep

Vinaya Ramesh Soundararajan and Anna Fishbein

Sleep and Food Allergy

Although the link between food allergy and sleep seems unlikely, there is some intriguing epidemiology which suggests that shortened sleep duration and poor sleep quality (i.e., snoring and frequent awakenings) are associated with increased odds of food allergy. This connection was first investigated in 2011 in China with adolescents between 12 and 21 years [1]. Short sleep duration (<6.8 h) was associated with the highest incidence of food sensitization (odds ratio, 95% confidence interval = 1.9, 1.3–2.7) or peanut sensitization (2.4, 1.5–3.8). Although this study did not determine if patients had clinical allergy, it raised an important question about whether improving sleep could be a simple intervention to decrease the risk of food allergy. This question has yet to be answered.

This group expanded work to toddlers and found that in a questionnaire-based study, snoring and nocturnal awakenings were associated with increased odds of food sensitization (odds ratio, 95% confidence interval = 4.31, 1.23–15.14, and 3.92, 1.00–15.35, respectively) [2]. Although the cross-sectional design of these studies makes it difficult to determine a causal relationship, snoring creates a state of hypoxemia, which increases IL-6 and TNF-α. Like other pro-inflammatory cytokines, these are also thought to increase risk of immune disease.

Although food allergy does not contribute to upper airway obstruction, it likely reflects an increased predisposition to atopy and allergic rhinitis. An Italian epidemiology study found that children under 36 months with food allergy were more likely to have a sleep disorder 8–10 years later [3]. Those sensitized to food had a higher incidence of being a habitual snorer, categorized as snoring more than three nights per week. Those with both food and inhalant allergies had even higher odds.

Circadian Rhythm and Food Allergy

The hypothesis of poor sleep quality via circadian disruption inducing allergic disease is supported by one human study on shift workers in China [4]. Nurses with a weekly day/night shift rotation had increased risk of developing food allergy

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3–4 years after starting shift work, as compared to non-shift workers. Although human inflammatory data was not different between the shift and non-shift worker, they did find their mouse model of "shift work" (altered circadian rhythm) increased inflammation and intestinal epithelial permeability, resulting in increased risk of food allergy. Although there are large limitations with this study, such as their definition of food allergy and the lack of human inflammatory data to support their mouse hypothesis, it is a curious finding.

Time of day of food allergen (or any antigen) exposure can certainly affect the allergic reactivity [5]. As described in detail in the chapter on circadian immunology, most immune cell types (including mast cells) have circadian rhythm. A recent mouse study found that time of day of food allergen exposure might induce a more severe allergic response [5]. One explanation is that IgE expression and signaling on mast cell have time of day differences [6–8].

Benefits of New Food Allergy Guidelines for Sleep

As a side point, the UK-based Enquiring About Tolerance (EAT) trial that looked at early introduction of allergenic foods [9] recently published about the link between sleep and infant food introduction [10], early solid food introduction (at 3 months as opposed to around 6 months), increased sleep duration, and decreased awakenings. This suggests that new guidelines about early introduction of allergenic foods might have a nice benefit for families looking to improve sleep in their children.

Conclusion

The multiple comorbidities in children with food allergy, such as atopic dermatitis, allergic rhinitis, and asthma, place them at risk for sleep disturbance. Nocturnal antigen exposures on the skin from environmental food dust might also flare eczema and worsen sleep disturbance. As described above, the main articles on this topic support the hypothesis that shortened sleep duration, poor sleep quality, or circadian disruption increases the risk of food allergy through complex immunologic mechanisms that require further exploration.

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