

Prevention of allergic respiratory disease in infants: current aspects and future perspectives

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Purpose of review

Primary and secondary prevention of severe atopic disease exemplified by atopic asthma represents an increasingly prominent focus of research in paediatric allergy. We review below the rationale for this approach and recent progress in development and testing of a range of potential preventive strategies.

Recent findings

The principal areas reviewed relate to potential and currently available treatments targeting enhancement of overall immune functions, allergen-specific immunomodulation and respiratory viral infections, particularly during early childhood.

Summary

The scientific rationale for prophylaxis of atopic diseases via early intervention strategies targeting young children is increasingly supported by findings from the experimental and clinical literature and significant progress may be expected in the mid-term future.

Keywords

asthma, atopy, early childhood, immunomodulation, viral infection

Introduction

Traditional treatment paradigms for allergy focus principally on established disease. Increasingly, the search for more effective approaches is being directed towards selectively targeting individual steps in the allergy cascade, as opposed to continued reliance on less specific steroidal anti-inflammatory drugs. Moreover, as evidence accumulates that the reversibility of severe atopic diseases decreases over time after onset, increasing emphasis is being placed on prevention. The targets in this context are the process of primary allergic sensitisation itself, or halting of progression from early stage to persistent, severe disease. This review summarizes the conceptual framework underpinning this 'prophylactic' approach, and highlights recent publications relevant to this expanding area.

Postnatal development of immune function: transition from fetal to postnatal responder phenotype

It is well established that fetal life and early infancy are periods of reduced innate and immune competence relative to later ages [1,2^{*}]. This manifests as partial skewing towards Th2 immunity [3] but is accompanied by more generalized attenuation of overall immune (including Th1) functions [3]. Postnatal survival in the extrauterine environment necessitates general upregulation and qualitative rebalancing of immune function, in particular Th1 competence, and a broad literature suggests that this is driven via microbial exposure [4]. This maturation process, which underpins the atopy-modulatory effects of microbial exposure enshrined in the hygiene hypothesis [5], is orchestrated principally via the Toll-like receptors (TLR) expressed on cells throughout the innate immune system [6], in particular, on dendritic cells.

As a result of microbial contact, the capacity of the adaptive immune system to secrete both Th1 and Th2 cytokines increases during infancy, but the initial maturation rate is greater for Th2 cytokines, resulting in transient persistence of Th2 skewing. Several factors contribute to this persistence [7]. Of particular note, fetal dendritic cells typically express the DC2 phenotype [8], and remain at low numbers in the circulation in early infancy [9]. Additionally, maturation of dendritic cell networks in mucosal tissues (such as airways) progresses relatively slowly postnatally, and is driven by exposure to irritant stimuli including microbes [10–12].

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Abbreviations

GIT	gastrointestinal tract
ICS	inhaled corticosteroid
RSV	respiratory syncytial virus
SIT	subcutaneous immunotherapy
TLR	Toll-like receptor

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Genetic risk for atopy and postnatal maturation of immunocompetence

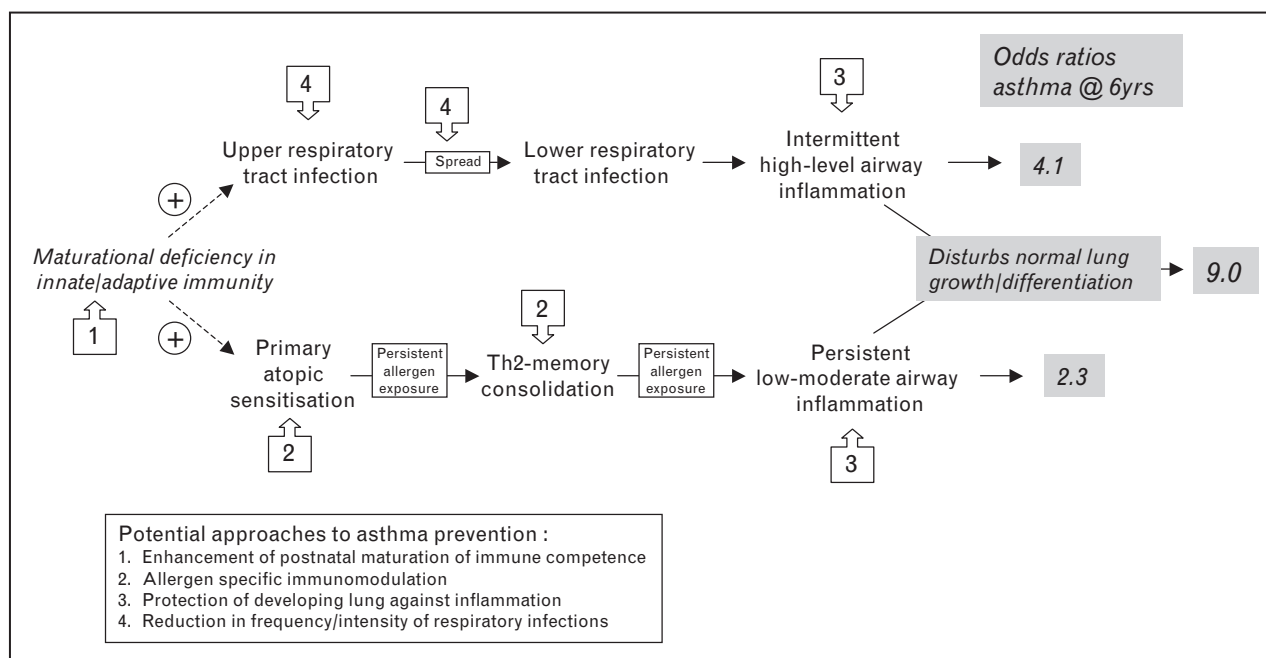
The postnatal maturation of immune function appears largely complete by the end of the preschool years, but certain specific activities exemplified by capacity of dendritic cells to produce IL-12 mature considerably more slowly and do not reach adult levels until the teens [13]. It is also clear that the majority of the developmental deficiencies in immune function are not absolute, and can be bypassed if primary signals of sufficient strength are presented to the immune system. An archetypal example is the strong Th1 immunity following bacillus Calmette–Guérin vaccination of infants [14] in contrast to the Th2-polarized responses elicited by the acellular diphtheria–pertussis–tetanus vaccine [15].

Nevertheless, the baseline T helper-polarity of the immune system during early life does appear to have potential consequences in relation to susceptibility to a variety of diseases. The notable example is risk for atopy, shown in [16] and multiple follow-on studies to be associated with exaggeration of the (developmentally) normal pattern of attenuated and Th2 polarized immunity during early life. Epidemiological evidence [17] additionally suggests that this same sluggish immune developmental phenotype may also be associated with risk for severe infections typified by respiratory syncytial virus (RSV). There is additionally plausible evidence that the downstream consequences of slow maturation of immunocompetence may include enhanced suscepti-

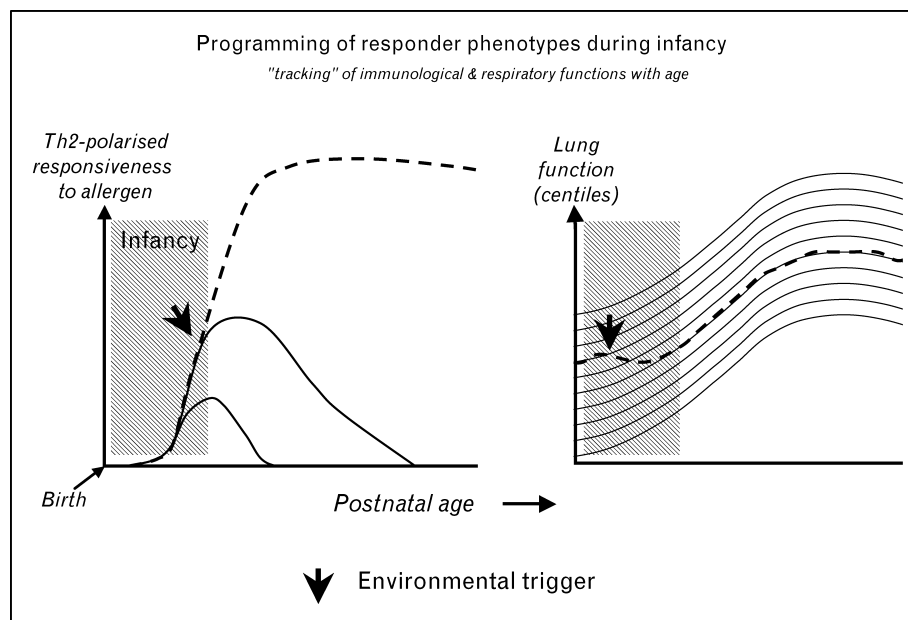
bility to development of persistent asthma [17], which is supported by several lines of investigation. Firstly, studies exemplified by those of Peat *et al.* [18] and Sherrill *et al.* [19] indicate that risk for later atopic asthma development is inversely related to age at initial sensitization. Secondly, in a large birth cohort of 2600 children, risk for asthma at age 6 years was doubled by atopic sensitization during the observation period, and increased by at least a further four-fold if the atopic children experienced more than one wheezing lower respiratory illness before age 2 years [20]. These and related findings have led to the development of a general model for the aetiology of persistent atopic asthma based on the combined effects of inflammation stemming from atopy and viral infection on the functional maturation of rapidly growing infant lung and airway tissues [17].

As illustrated in Fig. 1, atopic sensitization in early childhood and ongoing allergen exposure can independently lead to increased susceptibility to asthma which persists to age 6 but the associated odds ratios are modest. Viral infection, which spreads to the lower respiratory tract and intensifies sufficiently to trigger wheeze, leads to further increased risk, in particular multiple infections [20]. The occurrence of both sets of events in individual children, however, is associated with much higher odds ratios [20]. Moreover, susceptibility to proceeding down these risk pathways is determined by multiple genes, many of which (such as IFN γ , IL-12) are likely common to both pathways [17].

Figure 1 Model for asthma aetiology in early childhood



Odds ratios are derived from Oddy *et al.* [20] and are based on two or more wheezing lower respiratory infections by the second birthday.

Figure 2 Age dependent tracking of immunological function during childhood

The key concept underpinning this model, illustrated in Fig. 2, is the tracking over time of both immune and respiratory functions during childhood [17]. Earlier data [17] and our very recent findings [21^{*}] indicate that control of potentially pathogenic Th2 responses to allergens is normally achieved in early childhood via induction of immunological tolerance which is preceded by initial activation of T-help, often accompanied by transient Th2 cytokine and IgE production (bell-shaped tracks in Fig. 2 left; [21^{*}]). If this process is disturbed via some form of environment factor (arrow), the result can instead be consolidation of transient T-cell responses into Th2-polarized memory (broken line in left panel) which characterizes the atopic child [22]. This long-lasting responder phenotype has potential to damage airway tissues. Likewise, respiratory function in individual infants tracks stably within their respective (birth) population centiles during normal postnatal growth unless the underlying differentiation processes are disturbed sufficiently by adverse environmental influences such as inflammation [17]. As illustrated by the broken line in the right panel, tracking of respiratory function may then be dislodged (permanently) onto a lower centile. Thus, events occurring over relatively short periods during early childhood have the potential to program respiratory and immunological responder phenotypes, which may interact and manifest as disease (asthma) in later life. The mounting evidence that wheezing phenotypes manifesting in early childhood tend to track further towards young adulthood [23^{**}] provides a strong imperative for early intervention aimed at breaking this vicious cycle.

Prevention of persistent atopic disease by early intervention: theoretical options

The atopic disease of primary interest in the context of this review is persistent atopic asthma. The working model for asthma aetiology illustrated in Fig. 1 provides a conceptual framework for consideration of different classes of potential prevention strategies as follows.

Enhancement of postnatal maturation of immune functions

As noted above, this process is driven largely by signals from gastrointestinal tract (GIT) commensals, especially during infancy. The cellular targets are multiple including both innate and adaptive immune populations, and presumably rely upon TLR-signalling. Relevant approaches being tested include prebiotics and probiotics, microbial vaccines (in particular mycobacteria), and mixed bacterial extracts. In the main, these have been restricted to treatment of infants and young children, but modulation of immune development prenatally via treatment of mothers during late pregnancy has also been trialled.

Allergen-specific immunomodulation

Conventional immunotherapy targeted at increasingly younger age groups, aimed at desensitisation *per se* or at slowing progression from mild towards more severe atopic disease, is being widely practised. Recent promising findings in children as young as 3 years with sublingual immunotherapy (SLIT) [23^{**}] which circumvents problems associated with use of more traumatic subcutaneous immunotherapy (SIT) is fuelling a rapid expansion of interest in this approach.

A related but more radical approach is currently being tested in the authors' laboratories plus collaborating centres in Melbourne and New York via funding from the NIH Immune Tolerance Network (ITN; www.immunetolerance.org). This is based on concepts developed here [24] which suggested that sensitization to inhalant allergens during infancy was the result of a failure of mechanisms operative in the oropharyngeal and upper respiratory mucosa which normally promote development of immunological tolerance to locally deposited allergens. A similar process ('oral tolerance') is operative in the GIT and protects against food allergy. The concept being tested is that enhancing the intensity of allergen exposure of the oropharyngeal mucosa in high-risk infants employing a mixture of aeroallergens given repeatedly as sublingual drops will accelerate/enhance this tolerance process, thus reducing sensitization and atopic asthma. The defining difference between this and other immunomodulatory approaches is that the target here is immunoprophylaxis in subjects who are not yet sensitized. A comparable approach funded via ITN is being followed in London in relation to protection of high-risk children against peanut sensitization by repeated feeding during infancy. In both cases, results other than interim safety data will not be available for several years.

Protection of developing airways against inflammation

As indicated above, the highest risk for asthma results from the combined effects of airway inflammation arising from the viral or atopy pathways, and early use of anti-inflammatory drugs has the potential to attenuate the detrimental long term sequelae of such episodes. There has been a resurgence of interest recently in the early use of steroids in this context, and an expanding range of more selective drugs is becoming available. Based on our own recent findings pointing to the strength of the association between eosinophilia and asthma symptomatology in childhood [25], IL-5 inhibitors appear particularly interesting candidates in this context, although safety data relevant to very young age groups are not yet available. A less direct approach involves dietary manipulation to enhance availability of protective antioxidants [26].

Protection against the asthmatic effects of viral infections

Given the epidemiological evidence suggesting that airways inflammation resulting from viral infections contributes strongly towards asthma pathogenesis [18], prevention or attenuation of infections during infancy appears a valid option for asthma prevention. The challenge in this case is the paucity of appropriate antiviral therapeutics, although (as discussed below) the relevant cupboard is not entirely bare.

Recent developments

The concluding section of this review will focus on very recent publications relevant to the issues raised above.

The rationale for early intervention

Earlier indications [18,19] that the severity of the long-term sequelae of atopy is related to age of sensitization, are supported by more recent findings. In particular, we have recently reported that the synergistic interactions between early viral infections and atopic sensitization in relation to asthma risk was only seen if sensitization occurred prior to age 2 years [27^{••}]. Additionally, the earlier that children are sensitized, the more intense are their Th2 cytokine responses in later life [28[•]]. Furthermore, long-term follow-up of the Tucson birth cohort children has clearly demonstrated that children manifesting persistent wheeze by age 6 years maintain this phenotype into their late teens [29]. Collectively, these findings further support the notion that the key period for protection of high-risk children against the asthmatic effects of airway inflammation is during early childhood.

Should interventions start antenatally?

There is a continuing debate concerning precisely when the priming process underlying allergen-specific T-cell sensitization commences. In particular, a variety of earlier published studies on putative allergen-responsive T-cells in cord blood including our own (reviewed by Rowe *et al.* [21[•]]) concluded that T-cell priming may potentially occur via transplacental allergen transport. These findings have prompted suggestions that avoidance of certain allergens during pregnancy may be in high-risk situations. In a recent study [30], however, we demonstrated that T-cells responding to allergens in cord blood were naive immature thymic emigrants with modified antigen receptors which interact nonspecifically with protein antigens, as opposed to genuine T-memory cells. Consistent with suggestion, we recently demonstrated in a prospective cohort study that cord T-cell responses to mite allergen are unrelated to subsequent HDM-IgE production, and that stable Th-memory does not appear until beyond 6 months [21[•]]. In contrast, intrauterine T-cell priming clearly can occur in response to fetal virus infection or maternal vaccines [31], including influenza vaccination [32[•]]. The latter has been interpreted as support for fetal priming against environmental allergens, although this was not studied [32[•]]. Given the contrasting findings from direct investigations on neonatal T-cell responses to different classes of antigens [21[•],30], however, it is more plausible that fetal responsiveness to vaccines and pathogens is related to their much higher immunological potency and higher exposure doses, relative to the much lower immunogenic potential of inert allergens leaking from the maternal circulation. If this premise is accepted, then it can be argued that allergen-specific interventions should

only be initiated postnatally. This may not be the case, however, with respect to interventions targeted at innate immunity, given the recent report that maternal exposure to farming environmental factors, which protect offspring against atopy, was associated with upregulation of their TLR functions, and was most marked if maternal exposure occurred during, as opposed to after, pregnancy [33^{••}].

Developmental deficiencies in immune functions in high-risk infants: what targets and what treatments are feasible?

Over the last 15 years, the spectrum of immune functions shown to be developmentally constrained in the period of infancy during which allergen specific T-cell sensitization commonly occurs has expanded progressively. In particular, it has become evident that one of the key factors limiting the efficiency of T-cell immunity during infancy is innate immune function [2[•]]. A recent example is the demonstration that the principal factor limiting the in-vitro expression of Th-memory responses to vaccine was attenuated antigen presentation activity [34[•]]. The precise mechanisms involved are incompletely understood, but include serum carrier protein functions [35[•]] as well as mechanisms associated with intracellular signalling in dendritic cells [2[•]].

A number of studies have reported that these developmental deficiencies are more marked in high-risk infants, and these include observations related to Th-cells, monocytes and dendritic cell, and most recently T-regulatory cells [36]. A further addition to this list is the eosinophil progenitors, which exhibit a functionally immature phenotype in high-risk neonates associated with increased susceptibility to viral infections [37]. Given the increasing spectrum of cell types that appear to manifest maturational deficiencies in high-risk infants, it appears likely that the ultimate targets for immunostimulatory therapies may be early precursor populations, particularly in bone marrow.

In relation to testable treatments targeted at stimulating maturation of immune functions during infancy, there is continuing interest in interventions that seek to modulate GIT colonization with the commensals that normally drive this process. Earlier positive findings with probiotics in infants have stimulated numerous trials internationally, but the most recent crop of reports do not show consistent protection against atopy or atopic dermatitis [38[•]–41[•]] nor detectable effects on T-regulatory cell activity [42[•]], with one study [43[•]] reporting improvement in feeding tolerance in treated preterm infants who showed evidence of colonization with probiotic organisms. There is additionally interest in the use of 'prebiotic' oligosaccharides, the feeding of which enhances GIT colonization with commensal strains with immunomodulatory activity such as bifidobacteria [44[•]], and a recent study reported

reduction of atopic dermatitis in high-risk infants treated for 6 months with prebiotic [45[•]]. In this context, it is interesting to note the results of a large trial utilizing a more aggressive regimen involving prebiotic administration to women during the last month of pregnancy followed by combined prebiotic/probiotic treatment of their offspring, which demonstrated significant protection against eczema at age 2 years [46[•]], and this approach merits further investigation. In this context, it is pertinent to note recent experimental findings on postnatal acquisition of TLR4-mediated endotoxin tolerance in intestinal epithelial cells, a process that appears central to development of enteric host-microbe homeostasis [47^{••}]. Of particular interest was the finding that this process occurred rapidly in vaginally delivered mice but not in those delivered by Caesarean section [47^{••}]. These findings have a range of implications relevant to mechanistic studies on probiotic therapy, particularly the issue of the optimal timing of treatment and in relation to epidemiological findings on mode of birth as a risk factor for atopy.

Attempts have also been made to boost immune competence in school age children at high-risk of atopic dermatitis with more potent microbial stimuli derived from mycobacteria. Recent attempts to replicate earlier claims of clinical efficacy have yielded only modest positive effects [48[•]] or no effects greater than placebo [49[•]]. Whether such stimuli may be of more benefit in younger age groups remains an open question.

Targeting the induction and persistence of allergic sensitization

As noted above, the results of ongoing trials on primary prevention of sensitization of high-risk infants will not be known for several years. Results are flowing, however, from a range of studies focusing on later stages of the atopic march: attempts to reverse the allergic phenotype in children already sensitized. The rationale for this approach is the clear connection (reviewed in [50[•]]) between allergic rhinitis in childhood and subsequent bronchial asthma, arguing for early immunotherapy in rhinitic children to prevent later asthma onset. Further support for this concept has come from the 5-year follow-up of the European PAT study, confirming SIT-mediated protection of pollen allergic children from progression to asthma [51^{••}]. Moreover, earlier claims that SIT also protects against sensitization to 'bystander' allergens [52] have also gained further recent confirmation [53[•]].

The most intense current interest in this area focuses on the use of SLIT in children, and a range of reviews summarize recent findings [23^{••},54[•],55[•]]. While these studies are not universally positive [56[•],57[•]], the significant number which are [58[•]–61[•]] justify further vigorous pursuit of this approach.

Attempts to blunt the downstream asthmatic effects of airway inflammation by early use of anti-inflammatory drugs

As argued previously (Fig. 1; [17]), the highest odds ratios for early development of persistent asthma result from the combined effects of viral and inhalant allergy induced inflammation on lung growth and differentiation in the first few years of life. This is likely to be a cumulative process and hence reduction in the totality of the damage sustained during this period via use of anti-inflammatory drugs is potentially of benefit in relation to asthma prevention. The selection of appropriate drugs for use in the relevant age groups, however, represents a major unresolved issue. In this context, it is noteworthy that a recent large trial on 2-year treatment of high-risk children aged 2–3 years with inhaled corticosteroid (ICS) did not change subsequent development of asthma symptoms after treatment was stopped [62^{••}]. These findings are consistent with two previous studies [63[•], 64[•]] using long-term treatment with ICS in early childhood which failed to show disease modifying effects. While corticosteroids inhibit a broad range of effector mechanisms, their inhibitory effects are not universal and many pro-inflammatory genes are either spared or upregulated by corticosteroid, including genes operative in airway epithelial cells [65, 66[•]]. Moreover, we have demonstrated that postnatal development of the airway intraepithelial dendritic cell networks, which maintain immunological homeostasis in airway tissues, is disrupted by ICS [11, 67], and it is feasible that the negative effects of corticosteroids in this regard may outweigh any benefits flowing from their (incomplete) anti-inflammatory activity.

The cysteinyl leukotriene receptor antagonist montelukast has also been used in young children and shown to provide short-term symptom relief in asthma [68, 69[•]] and viral bronchiolitis [70], but did not protect against development of more persistent disease. What has yet to be trialled in this context are drugs selectively targeting individual components of the Th2-associated inflammatory cascade such as IL-4 and IL-5 antagonists and possibly anti-IgE. Lack of safety data in the relevant age groups, however, remains an issue.

It should be noted that there is also continued interest in the indirect dietary supplementation approach targeting anti-inflammatory n-3 polyunsaturated fatty acids [26], but the most recent trial [71[•]] did not confirm earlier positive findings in children.

Tackling the viral pathway

Inflammation airways of stemming from viral infection (Fig. 1) is an important contributor towards risk of early asthma development, and recent evidence demonstrates that the key viruses are RSV and rhinovirus [72^{••}]. It is

not currently feasible to accurately assess the relative contribution of each virus to this process at the population level, but both are clearly significant [27^{••}]. In relation to RSV, it has long been held that specific features of the virus (notably presence of the F protein) endows it with unique capabilities to stimulate Th2 immunity in a 'bystander' fashion and hence to interact directly with atopic processes, and recent evidence including demonstration of increased risk for hospitalization for RSV bronchiolitis in infants with atopic dermatitis [73[•]] and increased Th2 reactivity in infants following RSV infection [74] is consistent with this general hypothesis. There are currently no vaccines available for either virus, but there are indications that a live attenuated RSV vaccine may be available soon [75] and this will open up possibilities of *inter alia* infant protection via maternal immunization [76[•]]. In the case of RSV, a humanized monoclonal antibody is available which has proven effective in prevention of RSV bronchiolitis in high-risk infants, palivizumab [77]. Moreover, higher affinity version of the antibody known as Numax [78] has recently undergone trials in the northern and southern hemispheres, and one or more of these agents merits evaluation in high-risk infants as per Fig. 1.

In the case of rhinovirus, there appears little reason for hope of development of comparable tools in the foreseeable future, and the possibilities for potential control of infections with this pathogen are restricted to the use of other classes of antivirals. In relation to current availability, one approach that is testable is the use of orally delivered bacterial-derived broad-spectrum immunostimulants, which are in current use in paediatrics in other clinical settings. The two best known are OM-85 [79[•]] and Ribomunyl [80[•]]. OM-85 has a long history of use for prevention of infection-induced exacerbations in chronic obstructive pulmonary disease patients, including a successful multicentre trial in North America [81]. It has additionally been used extensively in young children for prevention of acute respiratory infections [82, 83]. Trials with Ribomunyl in children have reported comparable success particularly with respect to recurrent respiratory infections [80[•]] including in infants as young as 1 year [84].

Conclusion

In conclusion, the model for asthma aetiology summarized in Fig. 1 provides a useful framework for the rational design of interventions targeted at primary and secondary prevention of atopic disease. A variety of approaches appear justified by the forerunner literature and further supported by recently published data. This is becoming an increasingly active area of basic and clinical research, and there are grounds for optimism concerning potential developments in the mid-term future.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 594–595).

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