

Approach to Children with Recurrent Infections



Vivian P. Hernandez-Trujillo, MD^{a,b,*}

KEYWORDS

• Recurrent infections • Children • Immunodeficiency • Pediatric • Recurrent fever

KEY POINTS

- Frequent infections are common in young children, especially on first exposure to the day care or school setting.
- Severe infections that do not respond to traditional treatment can indicate a more serious underlying disorder of the immune system.
- Infections that are severe, persistent, unusual, or recurrent should be red flags to alert clinicians about patients who should have an immune work-up.
- Screening immune laboratory tests may be done initially, followed by a work-up guided by the type of infections, along with microorganism susceptibility.
- Prompt diagnosis and treatment are essential in minimizing the long-term effects from recurrent infections.

INTRODUCTION

Young children often present with a history of recurrent infections, especially once they are introduced to the day care or school setting. Children who present with recurrent infections before this introduction are even more concerning, particularly in children with failure to thrive or recurrent diarrhea. The childhood presentation of primary immunodeficiency diseases is common, although often misdiagnosed. Clinicians need to keep primary immunodeficiency in the differential diagnosis when caring for children who present with recurrent infections, particularly sinopulmonary infections. Campaigns have been created by the Immune Deficiency Foundation (IDF) and the

Disclosure: Advisory Board for Baxter Pharmaceuticals, CSL Behring, and Merck/Bayer; speakers bureau for Baxter Pharmaceuticals, CSL Behring; attendee at International Immune Globulin Conference, CSL Behring; research grant recipient, CSL Behring.

^a Division of Allergy and Immunology, Department of Pediatrics, Nicklaus Children's Hospital, 3100 Southwest 62 Avenue, Miami, FL 33155, USA; ^b Herbert Wertheim School of Medicine, Florida International University, Miami, FL 33199, USA

* Division of Allergy and Immunology, Nicklaus Children's Hospital, 3100 Southwest 62 Avenue, Miami, FL 33155.

E-mail address: Vivian.Hernandez-Trujillo@mch.com

Immunol Allergy Clin N Am 35 (2015) 625–636

<http://dx.doi.org/10.1016/j.iac.2015.07.005>

immunology.theclinics.com

0889-8561/15/\$ – see front matter © 2015 Elsevier Inc. All rights reserved.

Jeffrey Modell Foundation (JMF) to increase awareness regarding the diagnosis of primary immunodeficiency diseases.^{1,2}

SYMPTOMS/SIGNS

Patients with recurrent episodes of febrile illness may initially present with infections in any organ system.³ Most commonly, viral infections cause recurrent fever in young children.³ Although the most common presentation includes the sinopulmonary tract, infections can occur in any other organ system, commonly the gastrointestinal or mucocutaneous systems.⁴ If febrile episodes occur within specific time periods (ie, every week to 3 weeks), other diagnoses, such as periodic fever syndromes or cyclic neutropenia, should be considered.³

Recurrent sinopulmonary infections are a common hallmark in patients with recurrent infections. Recent studies show the role of CD4+ T-helper lymphocytes in protection against common organisms, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*.⁵ Pediatric patients with frequent otitis media (OM) infections were more likely to have lower levels of pneumococcal-specific immunoglobulin (Ig) G, as well as lower *S pneumoniae*-specific memory B cells, compared with children not prone to OM. Importantly, these patients also had lower levels of major histocompatibility complex II molecules on the surface of dendritic cells, which are potent antigen-presenting cells.⁵ These children, prone to OM, had poor responses to more than half the vaccine antigens studied. Children with frequent OM also had lower increases in antibodies between the ages of 6 and 24 months to *S pneumoniae* compared with children not prone to OM.⁵

Patients with recurrent infections may have other related disease, either gastrointestinal or respiratory. In some patients with recurrent OM, gastroesophageal reflux (GERD) is likely to play a role.⁶ Pepsin/pepsinogen was found in the middle ear of these patients, which may be related to GERD. The investigators found that GERD prevalence may be higher in patients with recurrent OM or chronic OM with effusion. In another study, structural airway abnormalities may have contributed to recurrent lower respiratory tract infections.⁷ In that study, 50% of children with lower respiratory tract infections also had tracheomalacia and/or bronchomalacia. Patients more often had positive bronchoalveolar lavage cultures to nontypable *H influenzae* or *S pneumoniae*.⁷

In children, urinary tract infections are the second most common bacterial infection.⁸ Urothelium expresses toll-like receptors that, when engaged, can result in inflammation, potentially leading to damage of the kidneys.⁸ A recent study in patients with vesicoureteral reflux showed that antimicrobial prophylaxis decreased the risk of recurrence of urinary tract infections.⁹ Patients with bladder and bowel dysfunction with index febrile infection benefited from antibiotic prophylaxis.¹⁰ Patients with recurrent infections of a particular location in the body (eg, urinary tract infections) may have deficiency of the innate or complement system (Fig. 1). Toll-like receptor 4 (TLR4) is essential in a patient's susceptibility to urinary tract infections.¹⁰ Patients with asymptomatic bacteriuria differed from those prone to recurrent acute pyelonephritis in that they had lower TLR4 expression in response to infection, suggesting that this attenuates the innate response at the mucosal level.¹⁰

Pediatric patients often present with group A streptococcus pharyngitis infections, and clinicians should consider whether the patient may be a carrier when the infections are recurrent. Treatment of carrier state may be helpful, whereas other patients may require tonsillectomy. One study compared children with recurrent community-acquired pneumonia that affected different lung areas with children who never had

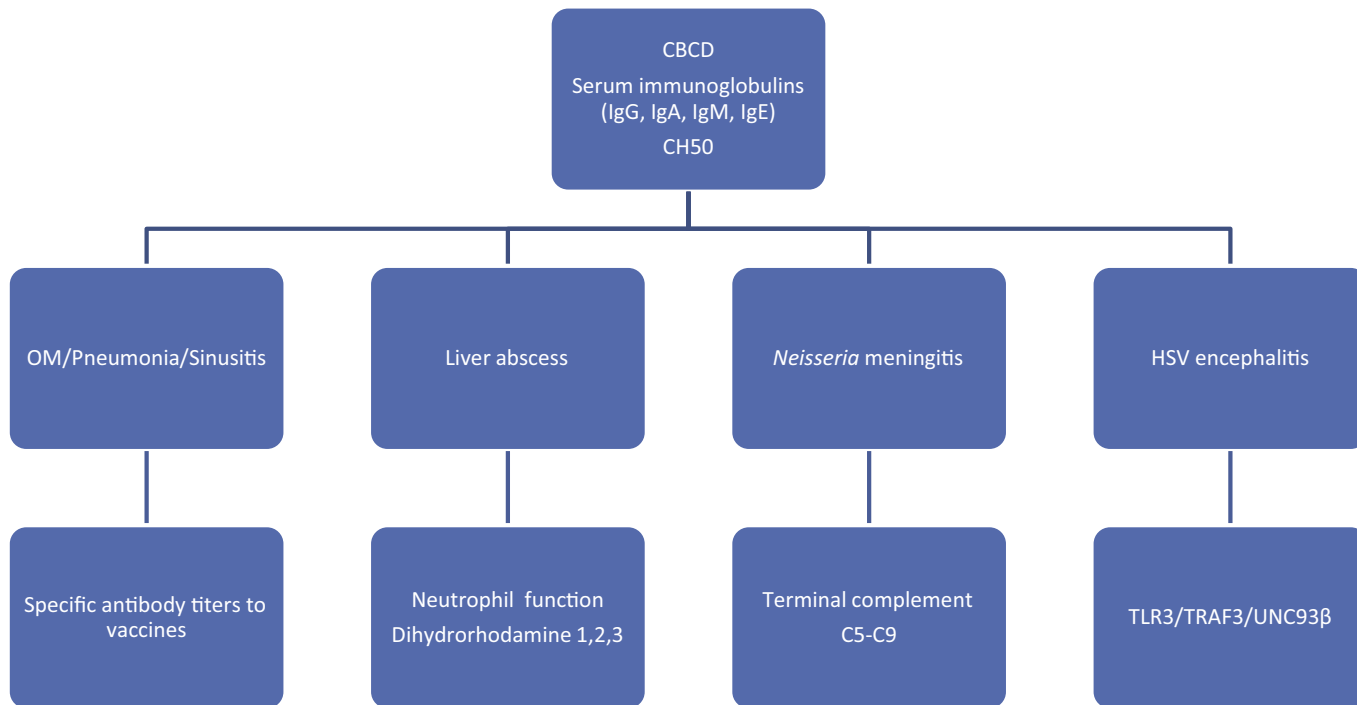


Fig. 1. Some primary immunodeficiencies can be diagnosed via a laboratory workup based on the site of infection. CH50, total complement hemolytic activity; HSV, herpes simplex virus; TLR3, toll-like receptor 3; TRAF3, tumor necrosis factor receptor-associated factor 3.

pneumonia.¹¹ The patients with recurrent community-acquired pneumonia were more likely to be premature, to have lower birth weight, to have a history of respiratory distress at birth, and to have started day care at an earlier age than control patients.¹¹ The investigators also described risk factors that are associated with community-acquired pneumonia recurrences, which include asthma, recurrent upper respiratory infections, atopy, chronic rhinosinusitis with postnasal drip, and wheezing.¹¹

Depending on the types of infections, presenting signs and symptoms may vary. Patients with recurrent fungal or viral infections may present with failure to thrive or chronic diarrhea.¹² Other patients may present with lymphadenitis or abscesses, which may be recurrent and severe. Still other patients may have difficulty with neisseria meningitis or recurrent infections caused by encapsulated organisms. Each of these presentations leads to a different diagnostic work-up.¹²

A campaign regarding the types of infections that should be red flags for patients with recurrent infections exists through the IDF.¹ Children with recurrent infections that are severe, persistent, unusual, recurrent, or that run in the family should be considered for a work-up for primary immunodeficiency. When an infection is severe, does not respond to traditional antibiotic or antifungal treatment, is unusual or recurrent, or is present in family members, laboratory tests should be ordered to investigate the immune system.

Criteria have also been developed by the JMF for warning signs that the immune system may be faulty (**Box 1**).² The criteria are important reminders of signs that may indicate defects in the patient's immune system. The number of ear or sinus infections within a year and the number of deep infections, such as abscesses or sepsis, are some of the warning signs. The need for intravenous antibiotics to clear infections is another criterion. Failure of children to gain weight and weight loss in adults are also important signs of possible immunodeficiency. A family history of primary immunodeficiency (PI) is also one of the criteria.

DIAGNOSTIC TEST/IMAGING STUDY

A basic immune screening includes a complete blood count with differential (CBCD) (**Box 2**). More extensive studies depend on the types of infections the child has had. In patients with recurrent bacterial infections, such as sinopulmonary infections like OM, sinusitis, or pneumonia, serum immunoglobulin levels (IgG, IgA, IgM, IgE) are an important screening tool.¹² In young children who have not received vaccines, isohemagglutinins may provide information regarding antibody function. More extensive studies to investigate antibody function are specific antibody levels to vaccines, such as diphtheria, tetanus, *H influenzae* type B, or *S pneumoniae* titers.^{12,13}

Administration of vaccines is a way to assess the patients' ability to produce antibodies.¹³ For assessment of protein antibody production, levels of antibodies to diphtheria and tetanus can be measured. For assessment of polysaccharide antibody production, levels of antibodies to *H influenzae* type B and *S pneumoniae* can be measured postvaccine, 4 weeks after the vaccine administration. In general, a 2-fold response compared with prevaccination titers is considered an adequate response to vaccination. If the titers are protective before vaccination, significant increases are less likely.¹³ Sometimes patients have an adequate antibody response with decreased clinical infections, but patients may develop recurrent infections after some time has passed from the vaccine administration.¹³ Because antibody levels decrease over time in healthy individuals, administration of a vaccine and assessment of the antibody response can help distinguish patients with immune defects from those with normal waning titers.

Box 1**JMF: 10 warning signs of primary immunodeficiency (PI)***Pediatrics*

1. Four or more new ear infections within 1 year
2. Two or more serious sinus infections within 1 year
3. Two or more months on antibiotics with little effect
4. Two or more pneumonias within 1 year
5. Failure of an infant to gain weight or grow normally
6. Recurrent deep skin or organ abscesses
7. Persistent thrush in mouth or fungal infection on skin
8. Need for intravenous antibiotics to clear infections
9. Two or more deep-seated infections including septicemia
10. A family history of PI

Adults

1. Two or more new ear infections within 1 year
2. Two or more new sinus infections within 1 year, in the absence of allergy
3. One pneumonia per year for more than 1 year
4. Chronic diarrhea with weight loss
5. Recurrent viral infections (colds, herpes, warts, condyloma)
6. Recurrent need for intravenous antibiotics to clear infections
7. Recurrent, deep abscesses of the skin or internal organs
8. Persistent thrush or fungal infection on skin or elsewhere
9. Infection with normally harmless tuberculosis-like bacteria
10. A family history of PI

These warning signs were developed by the Jeffrey Modell Foundation Medical Advisory Board. Consultation with primary immunodeficiency experts is strongly suggested. ©2009 Jeffrey Modell Foundation.

In patients with recurrent viral or fungal infections, the cellular immune system should be studied, including CBCD with special focus on absolute lymphocyte numbers, as well as lymphocyte enumeration (T, B, natural killer lymphocytes).¹² If these numbers are decreased, further laboratory investigation that assesses lymphocyte function, including proliferation to mitogens, should be ordered. In patients with recurrent lymphadenitis or abscess formation, neutrophil function should be evaluated with dihydrorhodamine 1,2,3 or oxidative burst. Patients with neisseria meningitis should be evaluated for complement deficiency with total complement hemolytic activity level (CH50).¹²

Box 2**General immune screening tests for recurrent infections**

Complete blood count with differential

Serum immunoglobulins (IgG, IgA, IgM, IgE)

Total complement hemolytic activity

In some patients, the site of the infection or the microorganism responsible for the infections aids the clinician in deciding which part of the immune system should be studied further¹⁴ (see **Fig. 1**; **Fig. 2**, **Table 1**). In patients with recurrent meningococcal infections, terminal complement levels (C5–C9) are helpful. Patients with recurrent salmonella or atypical mycobacterial infection may have deficiency of interleukin (IL) 12 β receptor or interferon gamma receptor,¹⁵ whereas those with recurrent pneumococcal infections may have deficiency of IL1 receptor–associated kinase 4 (IRAK4) or mutations in toll-like receptor 3 (TLR3), TRAF3 (tumor necrosis factor receptor–associated factor 3), and UNC93 β (UNC-93 homolog B1 [C elegans]) genes.^{14,16} Recurrent candida infections may be a clue that there is a susceptibility caused by a PI, with many possible defects responsible for the susceptibility (including STAT1, STAT3, IL17RA, IL17F, CARD9 [caspase recruitment domain member 9], dectin 1, IL22, IL12R β).^{17,18} Chronic mucocutaneous candidiasis has presentations that vary from being alone to presenting as part of a syndrome, such as autoimmune polyendocrinopathy candidiasis ectodermal dystrophy or hyper-IgE syndrome (HIES).^{17,19} In contrast, patients with persistent and symptomatic Epstein-Barr virus viremia may have CD27 deficiency.²⁰ Patients with problems caused by recurrent warts and hypogammaglobulinemia may have WHIM (warts, hypogammaglobulinemia, infections, and myelokathexis) syndrome,²¹ whereas those with monocytopenia and *Mycobacterium avium* complex may have MonoMac syndrome, and thus deficiency of Gata binding protein 2 (GATA-2) should be considered.²²

DIFFERENTIAL DIAGNOSIS

Some patients with recurrent OM have specific congenital disorders that are associated with recurrent OM.²³ These primary immunodeficiencies encompass different parts of the immune system, including diseases that affect antibody production, cellular disorders, and phagocytic disorders. Examples include X-linked agammaglobulinemia (XLA), common variable immunodeficiency (CVID), hyper-IgM syndrome, DiGeorge syndrome, ataxia telangiectasia, Wiskott-Aldrich syndrome, HIES, and chronic granulomatous disease (CGD).²³ These diseases should be kept in mind when assessing patients with recurrent OM.

Children may present with recurrent infections caused by other systemic diseases (**Box 3**). Gastroesophageal reflux that is severe can also lead to recurrent infections, both upper respiratory and OM.⁶ In children with a history of failure to thrive, poor weight gain, respiratory infections, and diarrhea, cystic fibrosis (CF) should be considered. Recurrent lung infections, particularly from *Pseudomonas aeruginosa* and *Staphylococcus aureus*, lead to loss in pulmonary function, and thus damage to the lungs.²⁴ Early diagnosis in the first 5 years of life, especially before the patients become symptomatic, is essential in preventing progressive lung disease. Screening tests, such as a sweat test or genetic testing, are available to screen for and diagnose CF. Other diseases to consider include ciliary dyskinesia, which can lead to recurrent sinopulmonary infections.²⁵ These patients present with recurrent OM or sinusitis that does not improve despite antibiotic treatment. Patients develop bronchiectasis. Some patients with ciliary dyskinesia have humoral immunodeficiency, and many have difficulties with *P aeruginosa* infections.²⁵ Ciliary biopsy can be done to aid in the diagnosis of this disease. Other patients, with diseases like alpha1-antitrypsin deficiency, present with recurrent respiratory infections like pneumonia, bleeding disorders, and liver disease.²⁶ The initial presentation may include respiratory symptoms, such as cough and shortness of breath. Later, the patients frequently develop emphysema and liver failure. Levels of alpha1-antitrypsin can be measured, followed by phenotype and genotype screening.^{26,27}

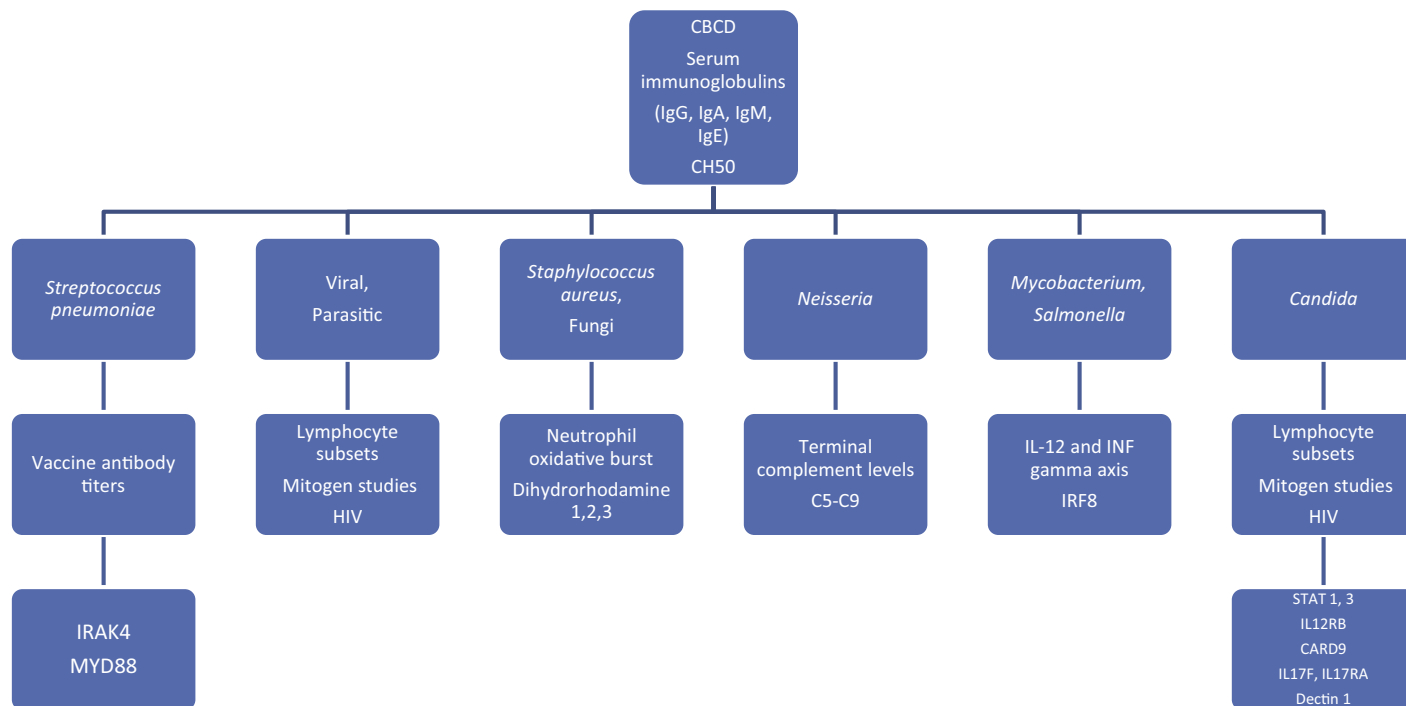


Fig. 2. Primary immunodeficiencies may present because of infections caused by specific microorganisms. In these patients, screening laboratory tests can be done, followed by work-up based on the organism and, in some cases, the genetic mutation leading to the infection. CARD9, caspase recruitment domain member 9; HIV, human immunodeficiency virus; IL, interleukin; INF, interferon; IRAK4, IL1 receptor-associated kinase 1; IRF8, interferon regulatory factor 8; MYD88, myeloid differentiation primary response gene 88; STAT, signal transducer and activation of transcription.

Table 1 Laboratory work-up based on location/type of infection and microorganism susceptibility		
CBCD, serum immunoglobulins Specific antibody to vaccines	Sinopulmonary	<i>S pneumoniae</i> , <i>Haemophilus influenzae</i> type B, Enterovirus
CBCD, lymphocyte subsets	Varies	Viruses, fungi, <i>Candida</i> , <i>Atypical mycobacterium</i> , <i>Pneumocystis jiroveci</i>
CBCD, serum immunoglobulins Lymphocyte subsets	Sinopulmonary	Bacteria, viruses, fungi, <i>P jiroveci</i> , parasites
CBCD, oxidative burst	Abscesses, lymphadenitis	<i>Staphylococcus aureus</i> , <i>Salmonella</i> , <i>Nocardia</i> , atypical mycobacteria Fungi: <i>Aspergillus</i>
Total complement	Meningitis	<i>Streptococcus</i> , <i>H influenza</i> type B, <i>Neisseria</i>

Patients with human immunodeficiency virus (HIV) also frequently present with recurrent infections, often viral or fungal. Children with congenital HIV may present with opportunistic infections.²⁸ Mothers infected with HIV have lower transplacental antibody transfer than mothers without HIV. In children without known HIV diagnosis, opportunistic infections are often the presenting symptom. In these children, maternally transferred antibodies can complicate the diagnosis of some infections.²⁸ Antiretroviral therapy helps within the first few months of treatment, and is important in improving CD4 counts and immune function. Patients who responded to highly active antiretroviral therapy (HAART) were more likely to have opportunistic infections and herpes zoster, Cytomegalovirus, and herpes simplex before HAART.²⁹ This finding is another reminder of the importance of proper diagnosis, as early as possible to ensure proper treatment.

TREATMENT

When patients have defects in antibody production, such as in XLA, CVID, hyper-IgM syndrome, and others, immune globulin replacement, available via intravenous and subcutaneous administration, is the treatment of choice.³⁰ Some patients also benefit from prophylactic antibiotics.¹² Patients with cellular defects may benefit from aggressive antibiotic treatment of infections or prophylaxis with antibiotics.¹² In contrast, some patients with complete DiGeorge syndrome/22q11 deletion benefit from thymic transplant.³¹ Patients with defective combined antibody and cellular defects, such as severe combined immunodeficiency, need more aggressive treatment, including immune globulin replacement, leading to stem cell transplant. Proper nutrition,

Box 3 Differential diagnosis in children with recurrent infections
Cystic fibrosis
Ciliary dyskinesia
Alpha1-antitrypsin deficiency
Gastroesophageal reflux
Human immunodeficiency virus (HIV1, HIV2)

aggressive treatment of infections, and prophylactic antibiotics are important in protecting the patients until they are able to receive their transplants.³²

Some patients with neutrophil disorders, like CGD, benefit from stem cell transplant, whereas others benefit from treatment with prophylaxis with itraconazole and trimethoprim/sulfamethoxazole.^{33,34} The use of gamma interferon to improve oxidative burst in these patients is also of benefit. Some newer studies are investigating gene therapy for these patients.^{35,36} Patients with terminal complement deficiency also benefit from prophylaxis with penicillin.¹²

For patients with CF, inhaled nebulized hypertonic saline, used to increase mucociliary clearance, along with antibiotic therapy, such as macrolide antibiotics, are important for the treatment of infections that can damage the lung, as well as for breaking up mucus.²⁴ Patients also benefit from chest physical therapy. Patients with ciliary dyskinesia should be treated aggressively with antibiotics, chest physical therapy and bronchodilators, and antiinflammatory medications.²⁵ Patients with alpha1-antitrypsin may require organ transplant for progressive lung or liver disease.²⁶ Some patients with Pi ZZ phenotype and forced expiratory volume in 1 second less than 65% benefit from intravenous alpha1-antitrypsin. Long-acting bronchodilators and inhaled corticosteroids are important in the treatment of the lung disease.²⁶ Influenza vaccinations yearly and pneumococcal vaccines every 5 years are also recommended. Patients with HIV can benefit from early combination retroviral therapy or HAART.^{28,29} Patients treated with HAART had few opportunistic infections.²⁹

MANAGEMENT

Long-term management should include careful monitoring by the primary care physician, along with the specialist, whether immunologist, pulmonologist, or gastroenterologist, depending on the disease responsible for the recurrent infections. The management is necessary in order to assess whether any change has occurred that may necessitate treatment, and to ensure that the patients are responding to therapy appropriately, if they are on a treatment plan.

Good nutrition, sleep, and exercise are also recommendations that are likely to benefit most patients with recurrent infections. Recommendations for overall maintenance of health may be useful, including regular use of hand washing, barrier techniques, and exercise. Use of hygiene measures has been shown to help prevent the spread of infections, both respiratory and gastrointestinal.^{36–40} Prevention of the spread of influenza has been seen with the use of face masks with hand hygiene in both home and community settings.^{36,37} Alcohol-based rub, foam, and wipes helped reduce the amount of virus from hands.³⁸ Moderate exercise has been shown to improve immune response to viral respiratory tract infections.⁴¹ The study also showed decreased inflammation from moderate exercise. Exercise also improves the immune response of the innate system.⁴² These recommendations are important for the overall health of the patients.

Interest in the use of probiotics in patients with recurrent infections has also grown. A recent meta-analysis found that probiotics were beneficial, compared with placebo, for prevention of recurrent infections.⁴³ The patients treated with probiotics had less antibiotic use and fewer episodes of acute upper respiratory tract infection. However, in some populations, the risk of sepsis exists if patients take probiotics, in particular in immunocompromised patients or premature infants.⁴³ Studies are needed regarding the use of probiotics in the treatment of upper respiratory tract infections.

Depending on the underlying disease that leads to recurrent infections, comanagement by the primary care physician and a specialist, either immunology for PI or

pulmonology and gastroenterology for CF or alpha1-antitrypsin deficiency, may be most helpful in attaining the best outcomes for the patients. Genetic counseling for patients who have a congenital or hereditary disease is also recommended.

SUMMARY

The approach to patients with recurrent infections should begin with a thorough history and physician examination, followed by screening laboratory tests. The types of infections, sites of infection, and microorganisms leading to infection are also helpful in guiding clinicians as to which parts of the immune system should be further studied. Immunology knowledge continues to expand, as new genetic diagnoses are added to the list of primary immunodeficiencies.^{44,45} The differential also includes common diseases that should be considered in patients with recurrent infections. Treatment should be targeted toward the particular disease that is causing the recurrent infections. Long-term management is essential in ensuring the health of any patient with chronic disease, in particular PI.

REFERENCES

1. Marshall GS. Prolonged and recurrent fevers in children. *J Infect* 2014;68:583–93.
2. Lehman H, Hernandez-Trujillo V, Ballow M. Diagnosing primary immunodeficiency: a practical approach for the non-immunologist. *Curr Med Res Opin* 2015;31:1–10.
3. Immune Deficiency Foundation. Available at: <http://primaryimmune.org/wp-content/uploads/2014/09/InfoCard.pdf>. Accessed March 11, 2015.
4. Jeffrey Modell Foundation. Available at: <http://www.info4pi.org/library/educational-materials>. Accessed March 11, 2015.
5. Sharma SK, Pichichero ME. Cellular immune responses in young children accounts for recurrent acute otitis media. *Curr Allergy Asthma Rep* 2013;13:495–500.
6. Miura MS, Mascaro M, Rosenfeld RM. Association between otitis media and gastroesophageal reflux: a systematic review. *Otolaryngol Head Neck Surg* 2012;146:345–52.
7. Santiago-Burruchaga M, Zalacain-Jorge R, Vazquez-Cordero C. Are airways structural abnormalities more frequent in children with recurrent lower respiratory tract infections? *Respir Med* 2014;108:800–5.
8. Mak RH, Kuo HJ. Pathogenesis of urinary tract infection: an update. *Curr Opin Pediatr* 2006;18:148–52.
9. RIVUR Trial Investigators. Antimicrobial prophylaxis for children with vesicoureteral reflux. *N Engl J Med* 2014;370:2367–76.
10. Ragnarsdottir B, Jonsson K, Urbano A, et al. Toll-like receptor 4 promoter polymorphisms: common TLR4 variants may protect against severe urinary tract infection. *PLoS One* 2010;5:e10734.
11. Patria F, Longhi B, Tagliabue C, et al. Clinical profile of recurrent community-acquired pneumonia in children. *BMC Pulm Med* 2013;13:60–8.
12. Bonilla FA, Bernstein IL, Khan DA, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *Ann Allergy Asthma Immunol* 2005;94:S1–63.
13. Ballow M. Use of vaccines in the evaluation of presumed immunodeficiency. *Ann Allergy Asthma Immunol* 2013;111:163–6.
14. Notarangelo LD. Primary immunodeficiencies. *J Allergy Clin Immunol* 2010;125(2 Suppl 2):S182–94.

15. Hambleton S, Salem S, Bustamante J, et al. Mutations in IRF8 and human dendritic cell immunodeficiency. *N Engl J Med* 2011;365:127–38.
16. Picard C, Casanova JL, Puel A. Infectious diseases in patients with IRAK-4, MyD88, NEMO or $\text{I}\kappa\text{B}\alpha$ deficiency. *Clin Microbiol Rev* 2011;24:490–7.
17. Kisand K, Peterson P. Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy and other primary immunodeficiency diseases help to resolve the nature of protective immunity against chronic mucocutaneous candidiasis. *Curr Opin Pediatr* 2013;25(6):715–21.
18. Puel A, Cypowyj S, Bustamante J, et al. Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. *Science* 2011;332:65–8.
19. Zhang Q, Su HC. Hyperimmunoglobulin E syndromes in pediatrics. *Curr Opin Pediatr* 2011;23:653–8.
20. Van Montfrans JM, Hoepelman AI, Otto S, et al. CD27 deficiency is associated with combined immunodeficiency and persistent symptomatic EBV viremia. *J Allergy Clin Immunol* 2012;129:787–93.
21. Tassone L, Notorangelo LD, Bonomi V, et al. Clinical and genetic diagnosis of warts, hypogammaglobulinemia, infections and myelokathexis syndrome in 10 patients. *J Allergy Clin Immunol* 2009;123:1170–3.
22. Bigley V, Collin M. Dendritic cell, monocyte, B and NK lymphoid deficiency defines the lost lineages of a new GATA-2 dependent myelodysplastic syndrome. *Haematologica* 2011;96:1081–3.
23. Urschel S. Otitis media children with congenital immunodeficiencies. *Curr Allergy Asthma Rep* 2010;10:425–33.
24. Grasemann H, Ratjen F. Early lung disease in cystic fibrosis. *Lancet Respir Med* 2013;1:148–57.
25. Boon M, De Boeck K, Jorissen M, et al. Primary ciliary dyskinesia and humoral immunodeficiency—Is there a missing link? *Respir Med* 2014;108:931–4.
26. Fregonese L, Stolk J. Hereditary alpha-1-antitrypsin deficiency and its clinical consequences. *Orphanet J Rare Dis* 2008;3:16–25.
27. Aboussouan LS, Stoller JK. Detection of alpha-1-antitrypsin deficiency: a review. *Respir Med* 2009;103:335–41.
28. Siberry GK, Abzug MJ, Nachman S, et al. Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children. *Pediatr Infect Dis J* 2013;32:1–10.
29. Nesheim SR, Hardnett F, Wheeling JT, et al. Incidence of opportunistic illness before and after initiation of highly active antiretroviral therapy in children in LEG-ACY. *Pediatr Infect Dis J* 2013;32:1089–95.
30. Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 2006;117:S525–53.
31. Markert ML, Devlin BH, McCarthy EA. Thymus transplantation. *Clin Immunol* 2010;135(2):236–46.
32. Cossu F. Genetics of SCID. *Ital J Pediatr* 2010;36:76–93.
33. Freeman AF, Holland SM. Antimicrobial prophylaxis for primary immunodeficiencies. *Curr Opin Allergy Clin Immunol* 2009;9(6):525–30.
34. Kaufmann KB, Chiriac M, Siler U, et al. Gene therapy for chronic granulomatous disease: current status and future perspectives. *Curr Gene Ther* 2014;14(6):447–60.
35. Griffith LM, Cowan MJ, Notorangelo LD, et al, workshop participants. Primary Immune Deficiency Treatment Consortium (PIDTC) report. *J Allergy Clin Immunol* 2014;133(2):335–47.

36. Cowling BJ, Chan KH, Fang VJ, et al. Facemasks and hand hygiene to prevent influenza transmission in households: a cluster randomized trial. *Ann Intern Med* 2009;151:437–46.
37. Wong VW, Cowling BJ, Aiello AE. Hand hygiene and risk of influenza virus infections in the community: a systematic review and meta-analysis. *Epidemiol Infect* 2014;142(5):922–32.
38. Larson EL, Cohen B, Baxter KA. Analysis of alcohol-based hand sanitizer delivery systems: efficacy of foam, gel, and wipes against influenza A (H1N1) virus on hands. *Am J Infect Control* 2012;40(9):806–9.
39. Jefferson T, Del Mar C, Dooley L, et al. Physical interventions to interrupt or reduce the spread of respiratory viruses. *Cochrane Database Syst Rev* 2010;(7):CD006207.
40. Sandora TJ, Shih MC, Goldmann DA. Reducing absenteeism from gastrointestinal and respiratory illness in elementary school students: a randomized, controlled trial of an infection-control intervention. *Pediatrics* 2008;121:e1555–62.
41. Martin SA, Pence BD, Woods JA. Exercise and respiratory tract viral infections. *Exerc Sport Sci Rev* 2009;37(4):157–64.
42. Woods JA, Vieira VJ, Keylock KT. Exercise, inflammation, and innate immunity. *Immunol Allergy Clin North Am* 2009;29:381–93.
43. Esposito S, Rigante D, Principi N. Do children's upper respiratory tract infections benefit from probiotics? *BMC Infect Dis* 2014;14:194–201.
44. Al-Herz W, Bousfiha A, Casanova JL, et al. Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency. *Front Immunol* 2014;5: 1–33.
45. Hernandez-Trujillo V. New genetic discoveries and primary immune deficiencies. *Clin Rev Allergy Immunol* 2014;46(2):145–53.