Approach to Children with Recurrent Infections

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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.

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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

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