Antimicrobial prophylaxis for primary immunodeficiencies

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Current Opinion in Allergy and Clinical Immunology 2009, 9:525–530

Purpose of review

Antibiotic prophylaxis is one of the mainstays of therapy of primary immunodeficiencies. We aim to summarize what is known about antibiotic prophylaxis for select primary immunodeficiencies.

Recent findings

In recent years, there has been a push towards more evidence-based practices for antimicrobial prophylaxis for many conditions such as antifungal prophylaxis for extremely premature neonates and antibiotic prophylaxis for neutropenia associated with chemotherapy. However, there are remarkably few data regarding antibiotic prophylaxis in primary immunodeficiencies and regimens vary greatly between practices.

Summary

Currently, antibiotic prophylaxis is guided by the common microbial pathogens seen in specific immunodeficiencies, and experience with other chronic illnesses such as cystic fibrosis, HIV, and immunosuppression from transplantation. Controlled studies are necessary to address the preferred antimicrobial and immunomodulator regimens for most of the primary immunodeficiencies.

Keywords

antibiotic prophylaxis, humoral defects, hyper-IgE syndrome, neutrophil defects, primary immunodeficiencies

Curr Opin Allergy Clin Immunol 9:525–530

1528-4050

Introduction

The HIV pandemic – an immune deficiency associated with discrete infections – spawned multiple prospective, well designed, robustly powered studies [1]. However, antimicrobial prophylaxis for the majority of other well studied conditions has rarely been studied in depth, let alone prospectively in a well powered way. Therefore, antimicrobial prophylaxis has been driven for years by clinical beliefs and clinical anxiety, but without much in the way of data-driven guidelines. Recently, some of the standard prophylactic practices have been questioned, along with the movement towards evidence-based practices. For example, there has been a recent marked decrease in the indications for endocarditis prophylaxis [2]. There has also been a reassessment of prophylactic antibiotics in vesicoureteral reflux [3], and some push away from prophylactic antibiotics for otherwise healthy children with recurrent otitis due to concerns of antimicrobial resistance [4]. In contrast, in other patient populations, there has been increasing evidence for prophylaxis including antifungals for extremely premature infants [5], and prophylactic antibiotics (typically a fluoroquinolone) during neutropenia associated with high-risk chemotherapy [6]. Importantly, in these studies the emergence of resistant organisms has been minimal. Despite the well recognized role of infections in primary immunodeficiencies and the wide conviction that they should be prevented with prophylactic antibiotics, there is a real dearth of evidence-based practices leading to marked variation between groups [7]. Therefore, in this review we will discuss antibiotic management and prophylaxis guided by the common infecting organisms in select primary immunodeficiencies.

Neutrophil defects

Chronic granulomatous disease (CGD) is characterized by an abnormal neutrophil respiratory burst due to defects of the NADPH oxidase, resulting in impaired neutrophil killing of select bacteria and fungi. Children with CGD usually present within the first few years of life with recurrent bacterial or fungal infections or tissue granuloma formation [8]. Typical pathogens in CGD patients are *Staphylococcus aureus*, *Nocardia* species, *Serratia marcescens*, *Burkholderia cepacia*, and *Aspergillus* species. Less frequent pathogens include other molds, other Gram-negative bacteria, and mycobacteria. Standard prophylactic treatment of CGD consists of a combination of antibiotics, antifungals, and interferon (IFN)-gamma [9]. Bone marrow transplantation can be curative.

 DOI:10.1097/ACI.0b013e328332be33

Chronic granulomatous disease is one of the few primary immunodeficiencies for which antimicrobial prophylaxis has been systemically studied. Trimethoprim-sulfamethoxasole (TMP-SMX, 6 mg/kg/day of trimethoprim divided twice daily) is the ideal antibacterial prophylactic agent as it has good activity against the most common bacterial pathogens of CGD, including *Nocardia* and community-acquired Methicillin-resistant *S. aureus* (MRSA) [9]. Studies have shown a decrease in bacterial infections in CGD while on TMP-SMX therapy from about one infection per year to about one every 4 years [10,11]. With the exception of *S. aureus*, the pathogens of CGD are environmental and not commensals of humans; therefore, antimicrobial resistance is rare. The best antibiotic for individuals with TMP-SMX allergy or intolerance is unclear. TMP-SMX desensitization should be considered when feasible. Second or third-generation cephalosporins can prevent most of the Gram-negative and methicillin-sensitive *S. aureus* infections. However, with increasing antibiotic resistance in community-circulating strains, this therapy may have limitations, and *Nocardia* may not be covered. Fluoroquinolones provide Gram-negative, and some *S. aureus* and *Nocardia* coverage; but toxicities including arthralgias and tendonitis and hypothetical concerns regarding long-term use in children may limit utility.

Until recently fungal infections were the leading cause of mortality in CGD. A placebo-controlled cross-over study of itraconazole prophylaxis showed marked efficacy against fungal infections in CGD [12]. Of the 39 enrolled patients, seven developed fungal infections while on placebo, whereas only one developed a fungal infection while on treatment. Plasma levels were checked due to the poor absorption of itraconazole in capsule form. Infections were prevented despite low plasma levels, suggesting that subtherapeutic or intermittent levels are effective for prophylaxis or that the critical prophylactic moiety is not properly measured as either itraconazole or dihydroitraconazole. At any rate, routine monitoring of levels during prophylaxis is not indicated. In the last several years, the use of oral voriconazole and posaconazole has increased. These antifungals have not been studied for prophylaxis in CGD, but likely have efficacy similar, if not better than itraconazole, as their spectrum of fungal coverage is broader and their absorption is better. Voriconazole and posaconazole prevent invasive mold infections in hematopoietic stem cell transplant populations [13]. Long-term therapy with voriconazole may be hindered by photosensitivity or hepatotoxicity; adherence to posaconazole may be hindered by its liquid formulation.

Less is known about antibiotics for the less common neutrophil defects. Leukocyte adhesion deficiency (LAD)-1 is characterized by delayed umbilical stump separation and omphalitis, severe gingivitis and periodontitis, skin infections with necrotic ulcerative lesions, and respiratory infections [14,15]. Pathogens in LAD-1 include *S. aureus*, Gram negatives, and oral flora, but not fungi. For those LAD-1 patients not transplanted, prophylactic antibiotics are typically used. Coverage of Gram negatives, oral flora and *S. aureus* should be considered. If MRSA is not present, amoxicillin/clavulanate or fluoroquinolones are reasonable. For other phagocytic defects, such as Chediak-Higashi and Griscelli syndromes, characterized by recurrent pyogenic infections, prophylactic therapy is typically individualized to the patient's infections.

Humoral immunodeficiencies

Humoral immunodeficiencies are characterized by chronic or recurrent ear, sinus, and lung infections predominantly with encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae* [16]. There is a spectrum of antibody deficiency included in this class, from the total absence of B cells and immunoglobulins in X-linked agammaglobulinemia (XLA), to the later presentations with more granulomatous complications in common variable immune deficiency (CVID). These immunodeficiencies are treated with replacement immunoglobulin. Use of prophylactic antibiotics varies widely, especially in CVID [17]. Some practitioners add prophylactic antibiotics if recurrent infections exceed three per year while on IVIG or if any severe infections occur [18•]; others provide prophylactic antibiotics to all individuals with severe antibody deficiencies on IVIG, whereas yet others only treat acute infections for individuals on IVIG. These variations in practice reflect the lack of controlled studies of prophylactic antibiotics in primary antibody deficiency disorders. Studies of prophylactic antibiotics decrease the number of otitis media recurrences in presumably immunocompetent children [19,20]. These studies used predominantly TMP-SMX or amoxicillin, both of which cover the predominant sinopulmonary pathogens, and suggest these may be appropriate choices for sinopulmonary infections from encapsulated bacteria [16]. Consistent use of one antibiotic is typically effective and associated with less resistance than the unsubstantiated practice of cycling antibiotics.

Although sinopulmonary infections predominate in humoral immunodeficiencies, XLA may be associated with neutropenia, leading to more serious staphylococcal or *Pseudomonas* infections; the neutropenia often resolves after IVIG replacement [16]. Giardia, mycoplasma and ureaplasma infections also occur in XLA, as well as persistent bacteremia and skin infections with *Helicobacter*-like organisms. Typically, prophylaxis for these organisms is not given, but accurate diagnosis and treatment are required. Chronic mycoplasma infections require prolonged treatment. Severe meningoencephalitic enteroviral infections are best prevented by maintenance of good replacement IVIG levels.

Individuals with CD40 ligand (CD40L) deficiency (X-linked hyper IgM syndrome), the most common of the immunoglobulin class switch defects, are predisposed to pyogenic sinopulmonary infections similar to those seen in XLA and successfully treated with immune globulin replacement. However, CD40L deficiency T cell defects predispose to *Pneumocystis jiroveci* (PCP), Cytomegalovirus (CMV), toxoplasmosis, cryptosporidiosis and sclerosing cholangitis [16]. Therefore, PCP prophylaxis is necessary, making TMP-SMX useful for PCP and pyogenic infection prevention. Avoidance of cryptosporidium-contaminated water is advisable. CMV is uncommon. Neutropenia associated with CD40L deficiency may require G-CSF.

Aggressive diagnosis and treatment of pulmonary infections prevent damage to the lung and resultant bronchiectasis. Unfortunately, bronchiectasis still develops in many antibody-deficient individuals. In addition to airway clearance techniques, trough IgG levels may be increased and prophylactic antibiotics aimed at recovered flora found in the sputum added. Organisms associated with cystic fibrosis (CF), such as *Pseudomonas*, *Aspergillus*, and nontuberculous mycobacteria, are infrequent in antibody deficiency-associated bronchiectasis, but careful microbiologic evaluation is necessary during pulmonary exacerbations [18•].

Azithromycin may improve lung function and decrease pulmonary exacerbations in both CF and non-CF bronchiectasis through its anti-inflammatory actions [21,22]. Although studies have not looked specifically at antibody deficiency, individuals with bronchiectasis and recurrent pulmonary exacerbations despite adequate immune globulin replacement may benefit from azithromycin, which is also active against mycoplasma.

For individuals with bronchiectasis and *Pseudomonas* colonization, inhaled antibiotics may be considered. In the US, the most experience is with inhaled tobramycin in CF resulting in improved pulmonary function, decreased bacterial load, and decreased hospitalizations [23]. In non-CF bronchiectasis, inhaled antibiotics may decrease the number of hospitalizations and microbial load, but not necessarily improve pulmonary function [23–26]. Intolerance of inhaled tobramycin frequently manifests as bronchospasm or hoarseness. Although acquired antimicrobial resistance has been demonstrated in some pathogens, no studies of inhaled antibiotics have focused specifically on primary immunodeficiencies.

Primary T cell immunodeficiencies

Severe combined immunodeficiency (SCID) arises from a growing list of genetic defects that cause severe deficiencies of number and/or function of T, B, and natural killer (NK) cells. SCID typically presents in the first few months of life with failure to thrive and recurrent viral, bacterial and candida infections resulting in death within the first year of life without definitive treatment [27]. Optimal management depends on early diagnosis and aggressive treatment and prevention of infections. Improved outcomes correlate with earlier diagnosis and definitive treatment, most commonly stem cell transplantation. Prophylaxis while awaiting definitive treatment is aimed at PCP (TMP-SMX) and immune globulin replacement. Fluconazole is frequently given to prevent mucocutaneous candidiasis and acyclovir to prevent herpes virus infection. If infections such as CMV are present, treatment should continue until definitive treatment (i.e. transplant) is performed. When BCG vaccination has been performed treatment should be given; nontuberculous mycobacteria (NTM) infections do not occur in SCID, so NTM prophylaxis is typically not needed. Live vaccines should be avoided, and all blood products should be CMV-negative and irradiated, or if not possible, leukocyte-depleted to minimize CMV transmission. Breast milk can transmit CMV, and some centers discourage breastfeeding until the CMV status of the mother is known.

DiGeorge syndrome is characterized by some combination of the following characteristics: immune dysfunction secondary to thymic hypoplasia, congenital heart defects, palatal abnormalities, hypocalcemia, characteristic facies and learning difficulties. The degree of immune dysfunction is variable and relates to the degree of impaired T cell development, although not necessarily the size of the thymus [28]; humoral defects are atypical. In severe thymic aplasia and profound T cell lymphopenia, which occur in less than 1% of DiGeorge cases, reprogramming of T cells through thymus transplant can be performed. However, for the majority of DiGeorge cases, immunodeficiency is not severe, may improve with age, and prophylactic antibiotics are often not necessary. Fewer opportunistic infections are seen in DiGeorge syndrome than in individuals with similar T cell numbers who have HIV. Most infections are upper respiratory tract infections, and may be due in part to structural abnormalities associated with the syndrome. Live viral vaccination should be avoided for individuals with severe T cell lymphopenia, but vaccination is recommended for those with more mild defects [29].

Hyper IgE syndrome

Autosomal dominant hyper IgE (Job's) syndrome (*STAT3*-deficient HIES) is characterized by *S. aureus* susceptibility with recurrent skin and lung infections, and a *S. aureus*-driven eczematoid rash [30]. Other pulmonary pathogens include pyogenic bacteria such as *S. pneumoniae* and *H. influenzae*. PCP may be the presenting pulmonary

infection, but is rare outside of infancy. Healing of pneumonias is often abnormal and bronchiectasis and pneumatocoeles may result, which are then sources of Gram-negative chronic infections (typically *Pseudomonas aeruginosa*), molds (*Aspergillus* and *Scedosporium*), or nontuberculous mycobacteria. Recurrent ear and sinus infections and mucocutaneous candidiasis are common. Infrequent but severe infections include extrapulmonary histoplasmosis, cryptococcosis, and coccidioidomycosis.

With the increasing frequency of community-acquired MRSA sensitive to TMP-SMX and the occurrence of PCP, TMP-SMX is an ideal prophylactic antibiotic for HIES. It is typically dosed at about 6 mg/kg/day of the TMP portion divided twice daily. With consistent adherence to this regimen, bacterial resistance is rare. Breakthrough infections should be cultured and therapy adjusted accordingly. Cycling of antibiotics has no advantage over use of one antibiotic consistently, and may lead to more resistance. Eczema driven by *S. aureus* may still occur despite appropriate antibiotics and responds quite well to dilute bleach baths (125 ml commercial bleach in a tub of water 15 min three times weekly) or frequent swimming in chlorinated pools.

The morbidity and mortality of HIES are typically associated with the structural lung defects that result after pyogenic bacterial infections. When bronchiectasis develops, colonizing organisms are similar to those of CF, with *Pseudomonas* predominating and eradication difficult. Nontuberculous mycobacteria and molds are also seen. Aspergillomas often develop in pneumatocoeles and may lead to vascular invasion with life-threatening hemoptysis or dissemination [31]. Therapy must be tailored to the colonizing species. Long-term therapy for fluoroquinolone-sensitive *P. aeruginosa* appears beneficial, but chronic toxicities from fluoroquinolones need to be considered. Azithromycin and inhaled tobramycin may be considered in bronchiectasis. If azithromycin is to be used, pulmonary nontuberculous mycobacterial infection should be excluded before inadvertant initiation of monotherapy. Inhaled tobramycin can cause airway irritation leading to bronchospasm and hemoptysis.

Mucocutaneous candidiasis and onychomycosis respond rapidly to fluconazole. *Aspergillus* associated with structural lung abnormalities in HIES are more worrisome and less well studied. Itraconazole prevents *Aspergillus* lung infections in CGD [12], whereas posaconazole and voriconzaole have been shown to work in hematopoietic stem cell transplant recipients [13]. In CGD and transplantation, however, the mold infections are parenchymal and invade structurally normal lung; mold infections in HIES occur in pneumatocoeles and bronchiectasis. A similar anatomy is seen in CF patients, who are at risk for allergic bronchopulmonary aspergillosis (ABPA). In ABPA, antiaspergillus azoles including itraconazole and voriconazole may improve symptoms and decrease exacerbations [32,33]. Lung transplant recipients also have increased risk of pulmonary aspergillosis and airway colonization. Voriconazole decreased invasive *Aspergillus* infections after lung transplant, although not necessarily *Aspergillus* colonization [34]. Also, inhaled amphotericin B can prevent invasive *Aspergillus* in lung transplant recipients [35], but the period of greatest risk for pulmonary aspergillosis is relatively short and thus treatment is for a finite time. Inhaled amphotericin may cause cough and increased irritation and may exacerbate hemoptysis. We typically treat individuals with *Aspergillus* infection with posaconazole due to its good long-term tolerability; however, eradication of *Aspergillus* infection and colonization in HIES is infrequent. For high-risk patients with significant structural lung disease we consider antifungal prophylaxis, typically with itraconazole or posaconazole.

Defects predisposing to disseminated nontuberculous mycobacterial infection: IL-12/IFN-gamma axis and NF-kB essential modulator

Defects of the IL-12/IFN-gamma axis predispose to NTM infections, as well as *Salmonella* and the endemic mycoses *Histoplasma*, *Coccidioides*, and *Paracoccidioides* [36]. Interferon-gamma receptor 1 mutations occur in dominant and recessive forms. In the dominant form there is diminished signaling through the IFN-gamma receptor, allowing focal mycobacterial disease, commonly due to BCG or *Mycobacterium avium* complex (MAC) osteomyelitis. In the recessive form there is no IFN-gamma receptor signaling with resultant severe disseminated mycobacterial disease. Antimicrobial treatment combined with IFN-gamma cytokine therapy is typically successful in treating the infection in the dominant form, following which secondary prophylaxis prevents future infections. Once the infection is definitively treated, azithromycin 250 mg orally daily alone appears adequate prophylaxis. IFN-gamma cytokine therapy can be used to augment treatment or prophylaxis in especially complex cases. In HIV-infected individuals, primary MAC prophylaxis is usually azithromycin dosed weekly (1200 mg) or twice weekly (600 mg) or clarithromycin dosed 500 mg twice daily [1]. Whether these HIV-based prophylactic strategies would be equally effective in autosomal dominant IFN-gamma receptor defects is unknown.

For complete recessive IFN-gamma receptor defects without residual signaling, initial infection occurs typically at a younger age, is disseminated, and relapses frequently after completion of therapy, suggesting that infection is rarely eradicated. Therefore, prolonged multidrug therapies are used. Stem cell transplantation

should be considered, but is risky after infection has been established. Interferon-alpha has been used to bypass some of the IFN-gamma receptor mediated defects [37].

NF-kB essential modulator (NEMO) deficiency is also characterized by susceptibility to NTM, but the spectrum of susceptibility to other infections is much broader than that in IFN-gamma and IL-12 defects and includes bacterial, viral, and *Pneumocystis* susceptibility [38]. Specific antibody production is often poor and patients typically require immune globulin replacement [17]. Prophylaxis for NTM, such as azithromycin, should be strongly considered as well as prophylaxis for other bacterial infections. Since *Pneumocystis* susceptibility is part of the syndrome, TMP-SMX is a logical choice, but these infections are uncommon outside of early childhood. Herpes family viral infections may require secondary prophylaxis.

Conclusion

Prophylactic and suppressive antimicrobials are being increasingly studied. However, controlled studies are lacking for most primary immunodeficiencies, leaving practices to be guided by clinical experience as well as experience in other disease populations, such as CF and HIV. The increase in community-acquired antimicrobial resistance may alter recommended antibiotics for prophylaxis, as well as the role of immunomodulators. Disease-specific studies focused on prevention of infection and its sequelae are needed to determine specific and successful therapies.

Acknowledgement

The research was supported by the Intramural Research Program of the NIH, NIAID, Bethesda, MD 20892. The views expressed in this article are those of the author and do not reflect the official policy of the U.S. Government.

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- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 575).

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