

## Bacterial Infections (Last updated November 6, 2013; last reviewed November 6, 2013)

### Panel's Recommendations

- Status of vaccination should be reviewed at every clinical encounter and indicated vaccinations provided, according to the established recommendations for immunization of HIV-infected children (**AIII**).
- Routine use of antibiotics solely for primary prevention of serious bacterial infections is not recommended (**BIII**). Discontinuation of antibiotic prophylaxis is recommended for HIV-infected children receiving antibiotics for the purpose of primary or secondary prophylaxis of serious bacterial infections once they have achieved sustained ( $\geq 3$  months) immune reconstitution: (CD4 T lymphocyte [CD4] cell percentage  $\geq 25\%$  if  $< 6$  years old; CD4 percentage  $\geq 20\%$  and CD4 count  $> 350$  cells/mm<sup>3</sup> if  $\geq 6$  years old) (**BII**).
- Intravenous immune globulin is recommended to prevent serious bacterial infections in HIV-infected children who have hypogammaglobulinemia (IgG  $< 400$  mg/dL) (**AI**).
- HIV-infected children whose immune systems are not seriously compromised (CDC Immunologic Category I) and who are not neutropenic can be expected to respond the same as HIV-uninfected children and should be treated with the usual antimicrobial agents recommended for the most likely bacterial organisms (**AIII**).
- Severely immunocompromised HIV-infected children with invasive or recurrent bacterial infections require expanded empiric antimicrobial treatment covering a broad range of resistant organisms (**AIII**).
- Initial empiric therapy for HIV-infected children with suspected intravascular catheter sepsis should target both gram-positive and enteric gram-negative organisms, with combinations that have activity against *Pseudomonas* spp. and methicillin-resistant *Staphylococcus aureus* (MRSA) (**AIII**).

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials *in children*<sup>†</sup> with clinical outcomes and/or validated endpoints; I\* = One or more randomized trials *in adults* with clinical outcomes and/or validated laboratory endpoints with accompanying data *in children*<sup>†</sup> from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies *in children*<sup>†</sup> with long-term outcomes; II\* = One or more well-designed, nonrandomized trials or observational studies *in adults* with long-term clinical outcomes with accompanying data *in children*<sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

<sup>†</sup> Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

## Bacterial Infections, Serious and Recurrent

### Epidemiology

Before combination antiretroviral therapy (cART) was available, serious bacterial infections were the most commonly diagnosed opportunistic infections in HIV-infected children, with an event rate of 15 per 100 child-years.<sup>1</sup> Pneumonia was the most common bacterial infection (11 per 100 child-years), followed by bacteremia (3 per 100 child-years), and urinary tract infection (2 per 100 child-years). Other serious bacterial infections, including osteomyelitis, meningitis, abscess, and septic arthritis, occurred at rates  $< 0.2$  per 100 child-years. Less serious bacterial infections such as otitis media and sinusitis were particularly common (17–85 per 100 child-years) in untreated HIV-infected children.<sup>2</sup>

Since the advent of cART, bacterial infections in HIV-infected children have decreased substantially,<sup>3,4</sup> and predominate in children who have not had a sustained response to cART.<sup>3</sup> The rate of pneumonia has decreased to 2 to 3 per 100 child-years,<sup>4-7</sup> similar to the rate of 3 to 5 per 100 child-years in HIV-uninfected children.<sup>8,9</sup> The rate of bacteremia/sepsis during the cART era also has decreased dramatically to 0.35 to 0.37 per 100 child-years,<sup>5,6,10</sup> but it remains substantially higher than that of invasive pneumococcal disease in U.S. children (0.018 and 0.0022 per 100 child years for those aged  $< 5$  and 5–17-year-olds, respectively).<sup>11</sup> Rates of sinusitis and otitis in cART-treated children are substantially lower than in the pre-cART era (2.9–3.5 per 100 child-years), but remain higher than those in HIV-uninfected children.<sup>6</sup>

## ***Pneumonia***

Acute pneumonia, often presumptively diagnosed in children, was associated with increased risk of long-term mortality in HIV-infected children in one study during the pre-cART era.<sup>12</sup> HIV-infected children not receiving cART who present with pneumonia are more likely to be bacteremic and to die than are HIV-uninfected children with pneumonia.<sup>13</sup> Children with chronic lung disease, including bronchiectasis, complicating repeated episodes of infectious pneumonia or lymphocytic interstitial pneumonitis,<sup>14</sup> are more susceptible to infectious exacerbations (similar to those in children and adults with bronchiectasis or cystic fibrosis) caused by typical respiratory bacteria (*Streptococcus pneumoniae*, non-typeable *Haemophilus influenzae*) and *Pseudomonas* spp.

### ***Streptococcus pneumoniae***

*S. pneumoniae* is the most prominent invasive bacterial pathogen in HIV-infected children both in the United States and worldwide, accounting for >50% of bacterial bloodstream infections in HIV-infected children.<sup>1,10,15-19</sup> HIV-infected children have a markedly higher risk of pneumococcal infection than do HIV-uninfected children.<sup>20,21</sup> In a Philadelphia cohort, the incidence of invasive pneumococcal disease (IPD) in HIV-infected children decreased by more than 80% from 1.9 per 100 patient-years before cART to 0.3 per 100 in the cART era.<sup>22</sup> The rate of hospitalization for IPD in HIV-infected children and youth also declined by nearly 80% since introduction of routine use of cART and pneumococcal conjugate vaccine.<sup>23</sup> In children with invasive pneumococcal infections, study results vary on whether penicillin-resistant pneumococcal strains are more commonly isolated from HIV-infected than HIV-uninfected patients.<sup>17,22,24,25</sup> Invasive disease caused by penicillin-nonsusceptible pneumococcus was associated with longer duration of fever and hospitalization but not with greater risk of complications or poorer outcome in a study of HIV-uninfected children;<sup>26</sup> however, most IPD in HIV-infected children is not caused by non-susceptible pneumococci.<sup>22</sup> In 2010, the 7-valent pneumococcal conjugate vaccine (licensed in 2000) was replaced by a 13-valent vaccine (including coverage for serotype 19A) for routine use in all children, including HIV-infected children.<sup>27</sup> The impact of routine use of 13-valent conjugate vaccine on invasive pneumococcal disease in HIV-infected children is not yet known.

### ***Haemophilus influenzae Type b***

HIV-infected children are at increased risk of *Haemophilus influenzae* type b (Hib) infection. In a study in South African children who had not received Hib conjugate vaccine, the estimated relative annual rate of overall invasive Hib disease in children aged <1 year was 5.9 times greater in those who were HIV-infected than those who were uninfected, and HIV-infected children were at greater risk for bacteremic pneumonia.<sup>28</sup> Hib infection is rare in HIV-infected children in the United States because routine Hib immunization confers direct protection to immunized HIV-infected children and herd immunity confers indirect protection.<sup>29</sup>

### ***Neisseria meningitidis (Meningococcus)***

HIV infection is associated with an increased risk of meningococcal disease.<sup>30,31</sup> In a population-based study of invasive meningococcal disease in Atlanta, Georgia,<sup>31</sup> as expected, the annual rate of disease was higher in 18- to 24-year-olds (1.17 per 100,000) than for all adults (0.5 per 100,000), but the estimated annual rate in HIV-infected adults was substantially higher (11.2 per 100,000). There are no studies of meningococcal disease risk in HIV-infected children in the United States. However, in a population-based surveillance study in South Africa, HIV infection significantly increased the risk of meningococcal bacteremia, which was associated with increased risk of death in all ages, but especially in children. Very few HIV-infected patients were receiving cART at the time of this study.<sup>30</sup>

### ***Methicillin-Resistant Staphylococcus aureus (MRSA)***

HIV infection appears to be a risk factor for MRSA infections in adults, but findings are conflicting about the relative contribution of immunosuppression vs. concomitant psychosocial risk factors to this increased risk.<sup>32-34</sup> Limited data suggest that HIV-infected children, like their uninfected counterparts, experience predominantly non-invasive, skin, and soft tissue infections as a result of community-associated MRSA strains and that greater immunosuppression may not confer greater risk of MRSA.<sup>35</sup>

## Other Pathogens

Other pathogens, including *Pseudomonas aeruginosa* and enteric organisms, cause infection in HIV-infected children, especially those who have indwelling vascular catheters or advanced immunosuppression or are not on cART.<sup>19,29,36,37</sup> The most commonly isolated pathogens in catheter-associated bacteremia in HIV-infected children are similar to those in HIV-negative children with indwelling catheters, including coagulase-negative staphylococci, *S. aureus*, enterococci, *P. aeruginosa*, gram-negative enteric bacilli, *Bacillus cereus*, and *Candida* spp.<sup>18,37</sup> In a cohort of 680 HIV-infected children in Miami, Florida, 10.6% had 95 episodes of gram-negative bacteremia between 1980 and 1997, of which only 6 were associated with an indwelling vascular catheter. The predominant organisms were *P. aeruginosa*, nontyphoidal *Salmonella*, and *Escherichia coli* (15%).<sup>29</sup> More than 70% had advanced immunosuppression and the overall case-fatality rate was 43%. In Kenyan children with bacteremia, HIV infection increased the risk of non-typhoidal *Salmonella* and *E. coli* infections.<sup>36</sup>

## HIV-Exposed (but Uninfected) Children

Data are conflicting about whether infectious morbidity increases in children who have been exposed to but not infected with HIV. In studies in developing countries, HIV-exposed but uninfected (HEU) infants had higher mortality (primarily because of bacterial pneumonia and sepsis) than did those born to uninfected mothers.<sup>38,39</sup> Advanced maternal HIV infection was associated with increased risk of infant death.<sup>38,39</sup> In a study in Latin America and the Caribbean, 60% of 462 HEU infants experienced infectious disease morbidity during the first 6 months of life, with the rate of neonatal infections (particularly sepsis) and respiratory infections higher than rates in comparable community-based studies.<sup>40</sup> However, in a study from the United States, the rate of lower respiratory tract infections in HEU children was within the range reported for healthy children during the first year of life.<sup>41</sup> There is increasing evidence for insufficient maternally derived antibody levels in HEU infants that put those infants at increased risk of pneumococcal and other vaccine-preventable infections.<sup>42</sup>

## Clinical Manifestations

Clinical presentation depends on the particular type of bacterial infection (e.g., bacteremia/sepsis, osteomyelitis/septic arthritis, pneumonia, meningitis, sinusitis/otitis media);<sup>43</sup> HIV-infected children with invasive bacterial infections typically have a clinical presentation similar to HIV-uninfected children.<sup>21,44,45</sup>

The classical signs, symptoms, and laboratory test abnormalities that usually indicate invasive bacterial infection (e.g., fever, elevated white blood cell count) are usually present but may be lacking in HIV-infected children who have reduced immune competence.<sup>21,43</sup> One-third of HIV-infected children not receiving cART who have acute pneumonia have recurrent episodes.<sup>12</sup> Bronchiectasis and other chronic lung damage that occurs before initiation of cART can predispose to recurrent pulmonary infections, even in the presence of effective cART.<sup>14</sup> Lower respiratory bacterial infections in children with lymphocytic interstitial pneumonitis (LIP) most often are a result of the same bacterial pathogens that cause lower respiratory infection in HIV-infected children without LIP and manifests as fever, increased sputum production, and respiratory difficulty superimposed on chronic pulmonary symptoms and radiologic abnormalities.<sup>46</sup>

In studies in Malawi and South Africa before the availability of cART, the clinical presentations of acute bacterial meningitis in HIV-infected and HIV-uninfected children were similar.<sup>47,48</sup> However, in a study from Malawi, HIV-infected children were 6.4-fold more likely to have repeated episodes of meningitis than were HIV-uninfected children, although the study did not differentiate relapses from new infections.<sup>47</sup> In both studies, HIV-infected children were more likely to die from meningitis than were HIV-uninfected children.

## Diagnosis

Attempted isolation of a pathogenic organism from normally sterile sites (e.g., blood, cerebrospinal fluid, pleural fluid) is strongly recommended, as identification and antimicrobial resistance testing will guide effective treatment.

Because of difficulties obtaining appropriate specimens, such as sputum, from young children, bacterial pneumonia most often is a presumptive diagnosis in children with fever, pulmonary symptoms, and an abnormal chest radiograph, unless an accompanying bacteremia exists. In the absence of a laboratory isolate, differentiating viral from bacterial pneumonia using clinical criteria can be difficult.<sup>8</sup> *Mycobacterium tuberculosis* (TB) and *Pneumocystis jirovecii* pneumonia (PCP) must always be considered in HIV-infected children with pneumonia. Presence of wheezing makes acute bacterial pneumonia less likely than other causes (e.g., viral pathogens, asthma exacerbation), atypical bacterial pathogens (e.g., *Mycoplasma pneumoniae*), or aspiration. Children with LIP often have episodes of bacterial respiratory infection superimposed on chronic wheezing. Sputum induction obtained by nebulization with hypertonic (5%) saline was evaluated for diagnosis of pneumonia in 210 South African infants and children (median age: 6 months), 66% of whom were HIV-infected.<sup>49</sup> The procedure was well-tolerated, and identified an etiology in 63% of children with pneumonia (identification of bacteria in 101, TB in 19, and PCP in 12 children). Blood and fluid from pleural effusion (if present) should be cultured.

In children with bacteremia, a source should be sought. In addition to routine chest radiographs, other diagnostic radiologic evaluations may be necessary in HIV-infected children with compromised immune systems to identify less apparent foci of infection (e.g., bronchiectasis, internal organ abscesses).<sup>50-52</sup> In children with suspected bacteremia and central venous catheters, blood culture should be obtained through the catheter and (if possible) peripherally; if the catheter is removed because of suspected infection, the catheter tip should be sent for culture.<sup>53</sup> Assays for detection of bacterial antigens or evidence by molecular biology techniques are important for diagnostic evaluation of HIV-infected children in whom unusual pathogens may be involved or difficult to identify or culture with standard techniques. For example, detection of *Bordetella pertussis* and *Chlamydomphila* (formerly *Chlamydia*) *pneumoniae* with polymerase chain reaction assays of nasopharyngeal secretions may aid in the diagnosis of these infections.<sup>8,54,55</sup>

## Prevention Recommendations

### Preventing Exposure

Because *S. pneumoniae* and *H. influenzae* (other than type b) are common in the community, no effective way exists to eliminate exposure to these bacteria. However, routine use of conjugated pneumococcal (initially 7-valent and, more recently 13-valent) and Hib vaccines in the United States has dramatically reduced vaccine-type nasopharyngeal colonization in healthy children, thus limiting the exposure of HIV-infected children to these pathogens (herd immunity).

### Food

To reduce the risk of exposure to potential GI bacterial pathogens, health-care providers should advise that HIV-infected children avoid eating the following raw or undercooked foods (including other foods that contain them): eggs, poultry, meat, seafood (especially raw shellfish), and raw seed sprouts (**BIII**). Unpasteurized dairy products and unpasteurized fruit juices also should be avoided (**BIII**). Of particular concern to HIV-infected infants and children is the potential for caretakers to handle these raw foods (e.g., during meal preparation) and then unknowingly transfer bacteria from their hands to children's food, milk or formula, or directly to the children. Hands, cutting boards, counters, and knives and other utensils should be washed thoroughly after contact with uncooked foods (**BIII**). Produce should be washed thoroughly before being eaten (**BIII**). These precautions are especially important for children who are not receiving effective cART.

### Pets

When obtaining a new pet, caregivers should avoid dogs or cats aged <6 months or stray animals (**BIII**). HIV-infected children and adults should avoid contact with any animals that have diarrhea and should always wash their hands after handling pets, especially before eating, and avoid contact with pets' feces (**BIII**). HIV-infected children should avoid contact with reptiles (e.g., snakes, lizards, iguanas, turtles) and with chicks



and ducklings (as well as their uncooked eggs) because of the risk of salmonellosis (**BIII**). These precautions are especially important for children who are not receiving effective cART.

### **Travel**

The risk of foodborne and waterborne infections in immunosuppressed, HIV-infected persons is magnified during travel to resource-limited settings. All children who travel to such settings should avoid foods and beverages that might be contaminated, including raw fruits and vegetables, raw or undercooked seafood or meat, tap water, ice made with tap water, unpasteurized milk and dairy products, and items sold by street vendors (**AIII**). Foods and beverages that are usually safe include steaming hot foods, fruits that are peeled by the traveler, bottled (including carbonated) beverages, and water brought to a rolling boil for 1 minute. Treatment of water with iodine or chlorine may not be as effective as boiling and will not eliminate *Cryptosporidia* but can be used when boiling is not practical. These precautions are especially important for children who are not receiving effective cART.

## ***Preventing Disease***

### **Immunization**

In addition to cART, one of the most important interventions to prevent bacterial infections in HIV-infected children is to ensure that they are immunized according to the HIV-specific recommended schedule ([Figures 1 and 2](#)) (**AII**). Vaccines that protect against bacterial pathogens directly (e.g., pneumococcal, Hib, meningococcal, pertussis) and indirectly (e.g., influenza) have been demonstrated safe and immunogenic in HIV-infected children.<sup>56-60</sup> HIV-infected children are at increased risk of under-immunization.<sup>61</sup> Status of vaccination against Hib, pneumococcus, meningococcus, pertussis, influenza, and all recommended vaccines should be reviewed at every clinical encounter and indicated vaccinations provided, according to the established recommendations for immunization of HIV-infected children (**AIII**). Effective cART instituted before immunization offers the best means to optimize response to immunization.<sup>62</sup> Lack of effective cART may reduce the magnitude, quality or duration of immunologic response and likely impairs memory response. Greater number or strength of vaccine doses are recommended in some circumstances to overcome suboptimal response. Evidence is mounting that protective immunity to vaccine-preventable disease is lacking in a high proportion of perinatally HIV-infected children who received many of their immunizations before the availability of effective cART.<sup>63</sup> These data suggest that HIV-infected children may benefit from assessment of seroprotection and/or re-immunization for certain vaccines.

### **Hib Vaccine**

HEU and HIV-infected infants and children aged  $\leq 5$  years should receive Hib vaccine on the same schedule as that recommended for healthy infants, including for catch-up immunization (**AII**). ([Figure 1](#)). Hib vaccine is recommended for routine administration to infants aged 2, 4, and 6 months (6-month dose not needed if PRP-OMP Hib conjugate vaccine used for 2- and 4-month doses), and 12 to 15 months; 1 to 3 doses are recommended for previously unvaccinated infants and children aged 7 to 23 months depending on age at first vaccination. Health-care providers should consider use of Hib vaccine for HIV-infected children aged  $\geq 5$  years who have not previously received Hib vaccine (**AIII**). For these older children, a single dose of any Hib conjugate vaccine is recommended.<sup>64</sup>

### **Pneumococcal Vaccines**

HEU and HIV-infected infants and children aged 2 to 59 months should receive the 13-valent pneumococcal vaccine (PCV13) on the same schedule as that recommended for healthy infants and children, including series completion for those who initiated immunization with PCV7 (**AII**).<sup>23,65,66</sup> A 4-dose series of PCV13 is recommended for routine administration to infants aged 2, 4, 6, and 12 to 15 months; 2 or 3 doses are recommended for previously unvaccinated infants and children aged 7 to 23 months depending on age at first vaccination.<sup>64</sup> Incompletely vaccinated children aged 24 to 71 months should receive 1 dose of PCV13 if 3 doses of PCV (7 or 13) were received previously, or 2 doses of PCV13  $\geq 8$  weeks apart if  $< 3$  doses of PCV (7

or 13) were received previously. Children who have received a complete series of PCV7 should receive a supplemental dose of PCV13 if they are aged 14 through 71 months. In addition, HIV-infected children aged  $\geq 2$  years should receive 23-valent pneumococcal polysaccharide vaccine (PPSV) ( $\geq 2$  months after their last PCV dose), with a single revaccination with PPSV 5 years later **(AII)**.<sup>57,64</sup> Data are limited regarding efficacy of PCV7 or PCV13 for children aged  $\geq 6$  years who are at high risk of pneumococcal infection. However, the U.S. Food and Drug Administration recently approved expanded use of PCV13 for children aged 6 to 17 years.<sup>67</sup> In addition, the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recently recommended that a single dose of PCV13 be routinely administered to children aged 6 years through 18 years with immunocompromising conditions who have not previously received PCV13.<sup>68</sup> Therefore, a single dose of PCV13 should be routinely administered to HIV-infected children aged 6 through 18 years who did not receive PCV13 before age 6 years<sup>64</sup> ([Figures 1 and 2](#)). A multicenter study of pneumococcal vaccination in a group of HIV-infected children not administered PCV during infancy demonstrated the safety and immunogenicity of 2 doses of PCV7 followed by one dose of PPSV for cART-treated HIV-infected children aged 2 to 19 years (including some who had previously received pneumococcal polysaccharide vaccination [PPSV]).<sup>57</sup> Based on this study, some experts recommend giving 2 doses of PCV13 to HIV-infected children aged  $\geq 6$  years who never received PCV7 or PCV13 **(BII)**. PPSV may be offered  $\geq 8$  weeks after PCV13 in children aged 6 to 18 years who received a PCV13 dose after having received PPSV **(CII)**.<sup>57</sup> The incidence of invasive pneumococcal disease was substantially lower in HIV-infected vaccine recipients in a placebo-controlled trial of a nine-valent PCV in South African children (most whom were not receiving antiretroviral therapy), but vaccine efficacy was somewhat lower in HIV-infected (65%) than HIV-uninfected children (85%).<sup>66</sup>

### **Meningococcal Vaccine**

Like healthy children, HIV-infected children should routinely receive meningococcal conjugate vaccine (MCV) at age 11 to 12 years and again at age 16 **(AII)**. In contrast to the 1-dose primary series for healthy children, the primary series of MCV for all HIV-infected children aged  $\geq 9$  months is 2 MCV doses at least 2 months apart for children aged 2 to 10 years, and 2 to 3 months apart for children aged 9 to 23 months in order to improve rates of seroprotection **(AII)**.<sup>64,69-71</sup> HIV-infected children aged 9 months to 10 years who have evidence of splenic dysfunction or complement deficiency or who plan to travel to high-incidence areas should receive the primary MCV series **(AIII)**. While ACIP does not list HIV infection as a specific indication for MCV, some experts give MCV to all HIV-infected children aged 9 months to 10 years because of the potentially increased risk of meningococcal disease **(CIII)**. HIV-infected children who receive their primary MCV series at ages 9 months to 10 years and who are at ongoing increased risk of meningococcal exposure should receive another MCV dose 3 years later (if primary MCV immunization was at ages 9 months to 6 years) or 5 years later (if primary MCV immunization was at  $\geq 7$  years) **(AIII)**.<sup>64</sup> MCV should be repeated every 5 years in children with splenic dysfunction or complement deficiency for as long as their splenic dysfunction persists **(AIII)**.

### **Influenza Vaccine**

Because influenza increases the risk of secondary bacterial respiratory infections,<sup>72</sup> annual influenza vaccination for influenza prevention can be expected to reduce the risk of serious bacterial infections in HIV-infected children **(BIII)** ([Figures 1 and 2](#)).<sup>73</sup> HIV-infected children should receive annual influenza vaccination according to the HIV-specific recommended immunization schedule **(AII)**.<sup>60,64</sup>

### **Chemoprophylaxis**

Trimethoprim-sulfamethoxazole (TMP-SMX) administered daily for PCP prophylaxis may decrease the rate of serious bacterial infections (predominantly respiratory) in HIV-infected children unable to take cART **(BII)**.<sup>16,74</sup> Atovaquone combined with azithromycin, which provides prophylaxis for *Mycobacterium avium* complex (MAC) as well as PCP, is well tolerated and as effective as TMP-SMX in preventing serious bacterial infections in HIV-infected children.<sup>75</sup> However, routine use of antibiotics solely for primary

prevention of serious bacterial infections (i.e., when not indicated for PCP or MAC prophylaxis or other specific reasons) promotes development of drug-resistant organisms and is not routinely recommended **(BIII)**. Intravenous immune globulin (IVIG) is recommended to prevent serious bacterial infections in HIV-infected children who have hypogammaglobulinemia (immunoglobulin G <400 mg/dL) **(AI)**.<sup>15</sup>

### ***Discontinuation of Primary Prophylaxis***

The Pediatric AIDS Clinical Trials Group (PACTG) 1008 demonstrated that discontinuation of MAC and/or PCP antibiotic prophylaxis in HIV-infected children who achieved sustained ( $\geq 16$  weeks) immune reconstitution (CD4 T lymphocyte [CD4] cell percentage  $>20\%$  to  $25\%$ ) while receiving ART did not result in excessive rates of serious bacterial infections.<sup>6</sup> HIV-infected children who are receiving an antibiotic for the purpose of primary prevention of serious bacterial infections should discontinue antibiotic prophylaxis once they have achieved sustained (i.e.,  $\geq 3$  months) immune reconstitution (CD4 percentage  $\geq 25\%$  aged  $<6$  years; CD4 percentage  $\geq 20\%$  or CD4 count  $>350$  cells/mm<sup>3</sup> if aged  $\geq 6$  years) **(BII)**.

## **Treatment Recommendations**

### ***Treating Disease***

The principles for treating serious bacterial infections are the same in HIV-infected and HIV-uninfected children. Specimens for microbiologic studies should be collected before initiation of antibiotic treatment. However, in patients with suspected serious bacterial infections, therapy should be administered empirically and promptly without waiting for results of such studies; therapy can be adjusted once results become available. The local prevalence of antibiotic-resistant bacteria (e.g., penicillin-resistant *S. pneumoniae*, MRSA) and the recent use of prophylactic or therapeutic antibiotics should be considered when initiating empiric therapy. When the organism is identified, antibiotic susceptibility testing should be performed, and subsequent therapy based on the results of susceptibility testing **(AIII)**.

HIV-infected children whose immune systems are not seriously compromised (CDC Immunologic Category I)<sup>76</sup> and who are not neutropenic can be expected to respond similarly to HIV-uninfected children and should be treated for the most likely bacterial organisms **(AIII)**. Based only on expert opinion, mild to moderate community-acquired pneumonia in HIV-infected children with only mild or no immunosuppression who are fully immunized (especially against *S. pneumoniae* and Hib) and who are receiving effective cART can be treated with oral antibiotics (usually oral amoxicillin), according to the same guidelines as for healthy children **(BIII)**.<sup>76</sup> However, many experts have a lower threshold for hospitalizing these children to initiate treatment. In addition, broader-spectrum antimicrobial agents for initial empiric therapy are sometimes chosen because of the potentially higher risk of non-susceptible pneumococcal infections in HIV-infected children.<sup>17,22,24,25</sup> Thus, options for empiric therapy for HIV-infected children outside of the neonatal period who are hospitalized for suspected community-acquired bacteremia or bacterial pneumonia include ampicillin or an extended-spectrum cephalosporin (e.g., ceftriaxone, cefotaxime) **(AIII)**.<sup>8,77,78</sup> The addition of vancomycin or other antibiotic for suspected bacterial meningitis should follow the same guidelines as for HIV-uninfected children.<sup>79</sup> The addition of azithromycin or other macrolide can be considered for hospitalized patients with pneumonia to treat other common community-acquired pneumonia pathogens (*M. pneumoniae*, *C. pneumoniae*). If MRSA is suspected or the prevalence of MRSA is high (i.e.,  $>10\%$ ) in the community, clindamycin (for non-CNS infections), doxycycline (non-CNS, for children aged  $>8$  years) or vancomycin can be added (choice based on local susceptibility patterns).<sup>80-82</sup> Neutropenic children also should be treated with an appropriate antipseudomonal drug with consideration for adding an aminoglycoside if infection with *Pseudomonas* spp. is likely. Severely immunocompromised HIV-infected children with invasive or recurrent bacterial infections require expanded empiric antimicrobial treatment covering a broad range of resistant organisms similar to that chosen for suspected catheter sepsis pending results of diagnostic evaluations and cultures **(AIII)**.

Initial empiric therapy for HIV-infected children with suspected intravascular catheter sepsis should target

both gram-positive and enteric gram-negative organisms, with combinations that include agents with anti-*Pseudomonas* activity and vancomycin, which is active against MRSA (AIII). Factors such as response to therapy, clinical status, identification of pathogen, and need for ongoing vascular access will determine the need for and timing of catheter removal.

### ***Monitoring and Adverse Events (Including IRIS)***

The response to appropriate antibiotic therapy should be similar in HIV-infected and HIV-uninfected children, with a clinical response usually observed within 2 to 3 days after initiation of appropriate antibiotics, recognizing that radiologic improvement in patients with pneumonia may lag behind clinical response. Whereas HIV-infected adults experience high rates of adverse and even treatment-limiting reactions to TMP–SMX, in HIV-infected children, serious adverse reactions to TMP–SMX appear to be much less of a problem.<sup>84</sup>

Immune reconstitution inflammatory syndrome (IRIS) has not clearly been described in association with treatment of bacterial infections in children. Reports of pneumonia, abscess and other bacterial infection in children during the first several weeks of effective cART have been attributed to IRIS<sup>85,86</sup> but are more likely related to persistent immune suppression. Suspicion of IRIS in a child being treated for a bacterial infection should raise concern for the presence of a different or additional infection or for inadequately treated infection mimicking IRIS.

### ***Preventing Recurrence***

Status of vaccination against Hib, pneumococcus, meningococcus, and influenza should be reviewed and updated, according to the recommendations outlined in the section Preventing First Episode of Disease and depicted in the immunization recommendation schedules ([Figures 1 and 2](#)) (AIII).

TMP-SMX (administered daily for PCP prophylaxis) and azithromycin or atovaquone-azithromycin (administered for MAC prophylaxis) also may reduce the incidence of serious bacterial infections in children with recurrent serious bacterial infections. Administration of antibiotic chemoprophylaxis to HIV-infected children who have frequent recurrences of serious bacterial infections despite cART (e.g., >2 serious bacterial infections in a 1-year period despite cART) can be considered (CIII); however, caution is required when using antibiotics solely to prevent recurrence of serious bacterial infections because of the potential for development of drug-resistant microorganisms and drug toxicity. In rare situations in which cART and antibiotic prophylaxis are not effective in preventing frequent recurrent serious bacterial infections, IVIG prophylaxis can be considered for secondary prophylaxis (CI).<sup>15</sup>

### ***Discontinuing Secondary Prophylaxis***

PACTG 1008 demonstrated that discontinuing MAC and/or PCP antibiotic prophylaxis in HIV-infected children who achieved sustained (i.e.,  $\geq 16$  weeks) immune reconstitution (CD4 percentage  $>20\%$  to  $25\%$ ) while receiving cART did not result in excessive rates of serious bacterial infections.<sup>6</sup> Antibiotics for secondary prophylaxis of serious bacterial infections should be discontinued in HIV-infected children who have achieved sustained (i.e.,  $\geq 3$  months) immune reconstitution (CD4 percentage  $\geq 25\%$  if  $\leq 6$  years old; CD4 percentage  $\geq 20\%$  or  $>350$  cells/mm<sup>3</sup> if  $>6$  years old) (BII).

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## Dosing Recommendations for Prevention and Treatment of Invasive Bacterial Infections

Indication	First Choice	Alternative	Comments/Special Issues
<b>Primary Prophylaxis</b> <i>S. pneumoniae</i> and other invasive bacteria	<ul style="list-style-type: none"> <li>• Pneumococcal, meningococcal, and Hib vaccines</li> <li>• IVIG 400 mg/kg body weight every 2–4 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• TMP-SMX 75/375 mg/m<sup>2</sup> body surface area per dose by mouth twice daily</li> </ul>	See Figures 1 and 2 for detailed vaccines recommendations.  <u>Vaccines Routinely Recommended for Primary Prophylaxis. Additional Primary Prophylaxis Indicated For:</u> <ul style="list-style-type: none"> <li>• Hypogammaglobulinemia (that is, IgG &lt;400 mg/dL)</li> </ul> <u>Criteria for Discontinuing Primary Prophylaxis:</u> <ul style="list-style-type: none"> <li>• Resolution of hypogammaglobulinemia</li> </ul> <u>Criteria for Restarting Primary Prophylaxis:</u> <ul style="list-style-type: none"> <li>• Relapse of hypogammaglobulinemia</li> </ul>
<b>Secondary Prophylaxis</b> <i>S. pneumoniae</i> and other invasive bacteria	<ul style="list-style-type: none"> <li>• TMP-SMX 75/375 mg/m<sup>2</sup> body surface area per dose by mouth twice daily</li> </ul>	<ul style="list-style-type: none"> <li>• IVIG 400 mg/kg body weight every 2–4 weeks</li> </ul>	<u>Secondary Prophylaxis Indicated:</u> <ul style="list-style-type: none"> <li>• &gt;2 serious bacterial infections in a 1-year period in children who are unable to take cART</li> </ul> <u>Criteria for Discontinuing Secondary Prophylaxis:</u> <ul style="list-style-type: none"> <li>• Sustained (≥ 3 months) immune reconstitution (CD4 percentage ≥25% if ≤6 years old; CD4 percentage ≥20% or CD4 count &gt;350 cells/mm<sup>3</sup> if &gt;6 years old)</li> </ul> <u>Criteria For Restarting Secondary Prophylaxis:</u> <ul style="list-style-type: none"> <li>• &gt;2 serious bacterial infections in a 1-year period despite cART</li> </ul>
<b>Treatment</b> Bacterial pneumonia; <i>S. pneumoniae</i> ; occasionally <i>S. aureus</i> , <i>H. influenzae</i> , <i>P. aeruginosa</i>	<ul style="list-style-type: none"> <li>• Ceftriaxone 50–100 mg/kg body weight per dose once daily, or 25–50 mg/kg body weight per dose twice daily IV or IM (max 4 g/day), or</li> <li>• Cefotaxime 40–50 mg/kg body weight per dose 4 times daily, or 50–65 mg/kg body weight 3 times daily (max 8–10 g/day) IV</li> </ul>	<ul style="list-style-type: none"> <li>• Cefuroxime, 35–50 mg/kg body weight per dose 3 times daily (max 4–6 g/day) IV</li> </ul>	For children who are receiving effective cART, have mild or no immunosuppression, and have mild to moderate community-acquired pneumonia, oral therapy option would be amoxicillin 45 mg/kg body weight per dose twice daily (maximum dose: 4 g per day).  Add azithromycin for hospitalized patients to treat other common community-acquired pneumonia pathogens ( <i>M. pneumoniae</i> , <i>C. pneumoniae</i> ).  Add clindamycin or vancomycin if methicillin-resistant <i>S. aureus</i> is suspected (base the choice on local susceptibility patterns).  For patients with neutropenia, chronic lung disease other than asthma (e.g., LIP, bronchiectasis) or indwelling venous catheter, consider regimen that includes activity against <i>P. aeruginosa</i> (such as ceftazidime or cefepime instead of ceftriaxone).  Consider PCP in patients with severe pneumonia or more advanced HIV disease.  Evaluate for tuberculosis, cryptococcosis, and endemic fungi as epidemiology suggests.

**Key to Acronyms:** cART = combination antiretroviral therapy; CD4 = CD4 T lymphocyte; IgG = immunoglobulin G; IM = intramuscular; IV = intravenous; IVIG = intravenous immune globulin; LIP = lymphocytic interstitial pneumonia; PCP = *Pneumocystis jirovecii* pneumonia; TMP-SMX = trimethoprim-sulfamethoxazole