

## ***Mycobacterium avium* Complex Disease** (Last updated January 8, 2019; last reviewed January 8, 2019)

### Panel's Recommendations

- I. **Is prophylaxis for *Mycobacterium avium* complex (MAC), with either clarithromycin, azithromycin, or rifabutin, indicated in children with HIV infection who have advanced immunosuppression to prevent MAC infection?**
  - Prophylaxis with either clarithromycin or azithromycin should be offered to children with HIV infection who have advanced immunosuppression (strong, low)
    - Children aged <1 year: <750 cells/mm<sup>3</sup>
    - Children aged 1 to <2 years: <500 cells/mm<sup>3</sup>
    - Children aged 2 to <6 years: <75 cells/mm<sup>3</sup>
    - Children aged ≥6 years: <50 cells/mm<sup>3</sup>
  - For children who cannot tolerate azithromycin or clarithromycin, rifabutin is an alternative prophylactic agent for MAC, although drug interactions and lack of efficacy data in children limit its use (weak, very low).
- II. **In children with HIV infection aged ≥2 years on stable antiretroviral therapy (ART) for ≥6 months and experiencing sustained (>3 months) CD4 T lymphocyte (CD4) cell count recovery, is discontinuation of primary prophylaxis associated with risk of disseminated MAC infection?**
  - Primary prophylaxis can be discontinued in children with HIV infection aged ≥2 years receiving stable antiretroviral therapy (ART) for ≥6 months and experiencing sustained (>3 months) CD4 count recovery well above the age-specific target for initiation of prophylaxis (i.e., as in adults, >100 cells/mm<sup>3</sup> for children aged ≥6 years [strong, high]; and >200 cells/mm<sup>3</sup> for children aged 2 to <6 years [strong, moderate]).
- III. **In children with HIV infection and MAC disease, is testing MAC isolates for susceptibility indicated to guide management?**
  - Testing of MAC isolates for susceptibility to clarithromycin or azithromycin is recommended (strong, very low).
- IV. **In children with HIV infection and MAC disease, does combination therapy with a minimum of 2 drugs compared with monotherapy prevent or delay the emergence of resistance?**
  - Combination therapy with a minimum of 2 drugs (e.g., clarithromycin or azithromycin plus ethambutol) is recommended to prevent or delay the emergence of resistance (strong, moderate). Monotherapy is associated with the emergence of high-level drug resistance.
- V. **In children with HIV infection and MAC disease, does the use of clarithromycin (as compared to azithromycin) improve clearance of bacteremia?**
  - There are insufficient data to recommend the use of clarithromycin over azithromycin. Some experts use clarithromycin as the preferred first agent, reserving azithromycin for patients with substantial intolerance to clarithromycin or when drug interactions with clarithromycin are a concern (strong, low).
- VI. **In children with HIV infection and MAC disease who are treated with combination therapy, does the addition of a third agent provide improved clearance of infection?**
  - Use of rifabutin as a third drug added to the macrolide/ethambutol regimen is controversial (weak, very low). Some experts would add rifabutin as a third drug to the clarithromycin/ethambutol regimen, particularly in the absence of ART and in the presence of high mycobacterial counts; however, with such combination therapy, drug interactions should be checked carefully, and more intensive toxicity monitoring may be warranted (strong, very low). Other experts recommend against using this third agent in children because of rifabutin's increased cytochrome P450 activity, which leads to increased clearance of other drugs such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, and the potential for increased toxicity associated with concomitant administration of drugs.
- VII. **In patients with HIV infection and MAC infection who are antiretroviral naive, what is the optimal timing to start ART to prevent IRIS?**
  - In patients with HIV and disseminated MAC disease who have not been previously ART treated, or are not receiving effective ART initiation, ART generally should be withheld until after the first 2 weeks of antimycobacterial therapy have been completed to reduce the risk of drug interactions and complications associated with IRIS and to lower the pill burden (weak, very low).
- VIII. **In patients with HIV infection and MAC infection who have failed treatment (defined as the absence of clinical response and the persistence of mycobacteremia after 8 to 12 weeks of treatment) is there an indication to repeat susceptibility testing to help guide clinical management?**
  - Treatment failure is defined as the absence of clinical response and the persistence of mycobacteremia after 8 to 12 weeks of treatment. Repeat susceptibility testing of MAC isolates is recommended in this situation, and a new multidrug regimen of two or more drugs not previously used, and to which the isolate is susceptible, should be administered (strong, very low). Drugs that should be considered for this scenario include rifabutin, amikacin, and a quinolone.

- X. In children with HIV infection with disseminated MAC and continued immunosuppression, does secondary prophylaxis prevent recurrence of infection?
- Children with a history of disseminated MAC and continued immunosuppression should receive lifelong prophylaxis to prevent recurrence (strong, low). Secondary prophylaxis typically consists of continued multidrug therapy used in treatment of disease.
- X. In children with HIV infection with disseminated MAC and sustained CD4 recovery, is discontinuation of secondary prophylaxis associated with risk of relapse?
- Some experts recommend discontinuation of therapy in children with HIV infection who meet all of the following criteria:
    - Aged  $\geq 2$  years and have completed  $\geq 12$  months of treatment for MAC;
    - Remain asymptomatic for MAC;
    - Receiving stable ART (i.e., ART not requiring change for virologic or immunologic failure);
    - Have sustained ( $\geq 6$  months) CD4 count recovery well above the age-specific target for initiation of primary prophylaxis (i.e., as in adults,  $>100$  cells/mm<sup>3</sup> for children aged  $\geq 6$  years [strong, low] and  $>200$  cells/mm<sup>3</sup> for children aged 2 to  $<6$  years [weak, very low]).

### Rating System

Strength of Recommendation: Strong; Weak

Quality of Evidence: High; Moderate; Low; or Very Low

## Epidemiology

*Mycobacterium avium* complex (MAC) refers to multiple related species of nontuberculous mycobacteria (NTM) (e.g., *Mycobacterium avium*, *Mycobacterium intracellulare*, and *Mycobacterium paratuberculosis*) that are widely distributed in the environment. Recent surveillance data have shown an increasing rate of MAC infection in some regions within the United States.<sup>1</sup> Comprehensive guidelines on the diagnosis, prevention, and treatment of nontuberculous mycobacterial diseases were published in 2007.<sup>2</sup> These guidelines highlight the tremendous advances in mycobacteriology laboratory methods that have expanded the number of known NTM species from 50 in 1997 to 125 in 2006. In the United States, NTM infections outnumber *Mycobacterium tuberculosis* infections and have become an important cause of pulmonary morbidity in adults.<sup>3</sup> In children, it appears that the overall prevalence of NTM is increasing over time.<sup>4,5</sup> Disseminated NTM is rare in children who are immunocompetent.

Before the advent of antiretroviral therapy (ART), MAC was second only to *Pneumocystis jirovecii* pneumonia among opportunistic infections (OIs) in children with HIV infection in the United States. With the availability of ART, the incidence of MAC has greatly decreased from 1.3 to 1.8 episodes per 100 person-years in the pre-ART era to 0.14 to 0.2 episodes per 100 person-years in the ART era.<sup>6,7</sup> MAC is ubiquitous in the environment and presumably is acquired by routine exposures through inhalation, ingestion, or inoculation.<sup>8</sup> A population-based study of adults and children in Florida associated soil exposure, black race, and birth outside the United States with MAC infection.<sup>9</sup> Respiratory and gastrointestinal (GI) colonization can act as portals from which infection can disseminate.<sup>10</sup>

MAC can appear as isolated lymphadenitis in children with and without HIV. Disseminated infection with MAC in pediatric HIV infection rarely occurs during the first year of life; its frequency increases with age and declining CD4 T lymphocyte (CD4) cell count but can occur at higher CD4 counts in younger children with HIV than in older children or adults with HIV. MAC is a recognized complication of advanced immunologic deterioration among children with HIV infection.<sup>8,11,12</sup>

## Clinical Manifestations

Respiratory symptoms are uncommon in children with HIV infection who have disseminated MAC, and isolated pulmonary disease is rare. Early symptoms can be minimal and may precede mycobacteremia by several weeks. Symptoms commonly associated with disseminated MAC infection in children include persistent or recurrent fever, weight loss or failure to gain weight, sweats, fatigue, persistent diarrhea, and

persistent or recurrent abdominal pain. Mesenteric adenitis may mimic acute appendicitis. GI symptoms can occur alone or in combination with systemic findings. Lymphadenopathy, hepatomegaly, and splenomegaly may occur. Laboratory abnormalities include anemia, leukopenia, and thrombocytopenia. Although children with disseminated MAC usually have normal serum chemistries, some children may have elevated alkaline phosphatase or lactate dehydrogenase levels. However, even in the absence of disseminated MAC, these signs and symptoms are relatively common in children with HIV and advanced immunosuppression.

## Diagnosis

Procedures used to diagnose MAC in children with HIV infection are the same as those used for adults with HIV infection.<sup>13</sup> MAC is definitively diagnosed by isolation of the organism from blood or from biopsy specimens from normally sterile sites (e.g., bone marrow, lymph node). Blood cultures are a sensitive and minimally invasive technique for the diagnosis of disseminated MAC as >90% of individuals in whom MAC is diagnosed have positive blood cultures.<sup>2,14</sup> Multiple mycobacterial blood cultures over time may be required to yield a positive result. The volume of blood sent for culture also influences yield, with increased volume leading to increased yield. Use of a radiometric broth medium or lysis-centrifugation culture technique can enhance recovery of organisms from blood. Nucleic acid probes that can identify MAC isolates once growth is detected are also commercially available. These organisms can also be rapidly identified by their mycolic acid patterns from the same samples by high-performance liquid chromatography, though this diagnostic technique may only be available at high volume laboratories.

Histology demonstrating macrophage-containing acid-fast bacilli is strongly indicative of MAC infection in a patient with typical signs and symptoms, but culture is essential to differentiate nontuberculous mycobacteria from *M. tuberculosis*, to determine which nontuberculous mycobacterium is causing infection, and to perform drug-susceptibility testing. Testing of MAC isolates for susceptibility to clarithromycin or azithromycin is most useful as clinical response is correlated with macrolides susceptibility.<sup>2</sup> As with tuberculosis testing, multiplex polymerase chain reaction testing platforms have been developed for rapid identification and drug susceptibility testing, but these technologies are currently only available in research laboratories.<sup>15-17</sup>

Although detection of MAC in stool or the respiratory tract may precede disseminated disease, no data demonstrate a correlation between initiation of prophylaxis in patients with detectable organisms at these sites and reduced risk of developing disseminated MAC.

## Prevention Recommendations

### *Preventing Exposure*

MAC is ubiquitous in the environment. Available information does not support specific recommendations regarding exposure avoidance.<sup>1</sup> Person-to-person transmission is not believed to be common.

### *Preventing First Episode of Disease*

The most effective way to prevent disseminated MAC in children with HIV infection is to preserve immune function through use of effective ART. Children with HIV infection who have advanced immunosuppression should be offered prophylaxis against disseminated MAC disease according to the CD4 count thresholds for children. Before prophylaxis is initiated in at-risk children, disseminated MAC disease must be ruled out, which includes obtaining a blood culture for MAC.<sup>2</sup>

## Treatment Recommendations

### *Treating Disease*

Disseminated MAC infection should be treated in consultation with a pediatric infectious disease specialist who has expertise in pediatric HIV infection. Combination therapy of MAC (with at least 2 drugs, typically

a macrolide and ethambutol) and improved immunologic status with ART is important for controlling disseminated MAC disease. Monotherapy with a macrolide results in emergence of high-level drug resistance within weeks.<sup>18</sup> Clarithromycin levels can be increased by protease inhibitors (PI) and decreased by efavirenz, but no data are available to recommend dose adjustments for children. Azithromycin is not metabolized by the cytochrome P450 (CYP450) system; therefore, it can be used without concern for significant drug interactions with PIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs).

The addition of rifabutin as a third drug to combination therapy of MAC is controversial. Rifabutin increases CYP450 activity that leads to increased clearance of other drugs (e.g., PIs, NNRTIs), which should prompt careful review of drug interactions if such drugs are administered concomitantly and may also warrant more intensive toxicity monitoring.<sup>19</sup> No pediatric formulation of rifabutin exists, but the drug can be administered mixed with foods such as applesauce. Rifabutin can also be compounded in a liquid formulation by a pharmacist. Limited safety data are available from a study in 22 children with HIV infection (median age: 9 years) who received rifabutin in combination with 2 or more other antimycobacterial drugs for treatment of MAC for 1 to 183 weeks; doses ranged from rifabutin 4 mg/kg to rifabutin 18.5 mg/kg, and reported adverse effects were similar to those reported in adults.<sup>20</sup> The most commonly reported dose in children has been rifabutin 5 mg/kg. Therapy is typically prolonged and depends upon response and immune reconstitution.

In the United States, treatment with ART has become the standard practice for all children with HIV. The optimal time to start ART in children with disseminated MAC is unknown; many experts treat MAC with antimycobacterial therapy for 2 weeks before starting ART to minimize immune reconstitution inflammatory syndrome (IRIS). For children already receiving ART, their ART regimen should be continued and optimized with careful attention to potential drug interactions between the ARV and antimycobacterial drugs.

### ***Monitoring and Adverse Events, Including IRIS***

Clinically, most patients improve substantially during the first 4 to 6 weeks of therapy. A repeat blood culture for MAC should be obtained 4 to 8 weeks after initiation of antimycobacterial therapy in patients who fail to respond clinically to their initial treatment regimen. Some experts would consider a repeat blood culture for all patients with an initial positive culture, regardless of clinical response to therapy. Improvement in fever can be expected within 2 to 4 weeks after initiation of appropriate therapy. However, for those with more extensive disease or advanced immunosuppression, clinical response may be delayed, and elimination of the organism from the blood may require up to 12 weeks of effective therapy.

Adverse effects from clarithromycin and azithromycin include nausea, vomiting, abdominal pain, abnormal taste, and elevations in liver transaminase levels or hypersensitivity reactions. The major toxicity associated with ethambutol is optic neuritis, with symptoms of blurry vision, central scotomata, and red-green color blindness, which usually is reversible and rare at doses of 15 to 25 mg/kg in children with normal renal function. The risks and benefits of using ethambutol in very young children whose visual acuity cannot be monitored must be carefully considered.<sup>21,22</sup>

Patients receiving clarithromycin plus rifabutin should be observed for the rifabutin-related development of leukopenia, uveitis, polyarthralgias, and pseudojaundice. Tiny, almost transparent, asymptomatic peripheral and central corneal deposits that do not impair vision have been observed in some children with HIV infection receiving rifabutin as part of a multidrug regimen for MAC.<sup>20</sup>

When deciding whether to begin immediate ART in children with very low CD4 counts, the urgent need for rapid immunologic improvement must be considered alongside the possibility of IRIS due to MAC. IRIS in patients receiving MAC therapy and ART has been reported in adults and children with HIV infection.<sup>23-26</sup> New onset of systemic symptoms, especially fever or abdominal pain, leukocytosis, and focal lymphadenitis (cervical, thoracic, or abdominal), associated with preexisting—but relatively asymptomatic—MAC infection have occurred after the start of ART (unmasking IRIS). In addition, paradoxical worsening of systemic or local symptoms of MAC may occur as the immune system is rapidly reconstituted. Mycobacteremia is typically absent.

## ***Managing Treatment Failure***

MAC treatment failure is defined as the absence of clinical response and the persistence of mycobacteremia after 8 to 12 weeks of treatment. Repeat susceptibility testing of MAC isolates is recommended in this situation, and a new multidrug regimen of two or more drugs not previously used, and to which the isolate is susceptible, should be administered. Drugs that should be considered for this scenario include rifabutin, amikacin, and a quinolone. Data from treating MAC in patients without HIV suggest the use of injectable agents such as amikacin or streptomycin may be additional considerations.<sup>2,3</sup>

## ***Preventing Recurrence***

Children with a history of disseminated MAC should be given prophylaxis to prevent recurrence until their immune systems are reconstituted. Prophylaxis in this setting means continuation of multidrug therapy because use of a single agent (clarithromycin or azithromycin) for secondary prophylaxis carries a high risk of inducing drug-resistant MAC infection.

## ***Discontinuing Secondary Prophylaxis***

On the basis of immune reconstitution data in adults<sup>21,27</sup> and data in children discontinuing primary prophylaxis, some experts recommend discontinuing secondary prophylaxis in children with HIV infection who are aged  $\geq 2$  years and have completed  $\geq 12$  months of treatment for MAC, remain asymptomatic for MAC, and are receiving stable ART (i.e., ART not requiring change for viral or immune failure) and who have sustained ( $\geq 6$  months) CD4 count recovery well above the age-specific targets for initiation of primary prophylaxis.

## **Primary Prevention**

### **I. Is prophylaxis for MAC with either clarithromycin, azithromycin, or rifabutin, alone, indicated in children with HIV infection who have advanced immunosuppression?**

- Prophylaxis with either clarithromycin or azithromycin should be offered to children with HIV infection who have advanced immunosuppression (**strong, low**)
  - Children aged <1 year: <750 cells/mm<sup>3</sup>
  - Children aged 1 to <2 years: <500 cells/mm<sup>3</sup>
  - Children aged 2 to <6 years: <75 cells/mm<sup>3</sup>
  - Children aged  $\geq 6$  years: <50 cells/mm<sup>3</sup>

Based on randomized controlled trials, clarithromycin and azithromycin are the preferred prophylactic agents for adults. While there are no randomized controlled trials in children, either agent is recommended for prophylaxis in children (**strong, low**); oral suspensions of both agents are commercially available in the United States. Combination therapy for prophylaxis generally should be avoided in children because it is not cost effective and increases the risk of adverse events (**strong, low**).

- For children who cannot tolerate azithromycin or clarithromycin, rifabutin is an alternative prophylactic agent for MAC, although drug interactions and a lack of efficacy data in children limit its use (**weak, very low**).

### **II. In children with HIV infection aged $\geq 2$ years on stable antiretroviral therapy (ART for $\geq 6$ months and experiencing sustained [ $>3$ months] CD4 T lymphocyte [CD4] cell count recovery), is discontinuation of primary prophylaxis associated with risk of disseminated MAC infection?**

- Primary prophylaxis can be discontinued in children with HIV infection aged  $\geq 2$  years receiving stable antiretroviral therapy (ART) for  $\geq 6$  months and experiencing sustained ( $>3$  months) CD4 count recovery well above the age-specific target for initiation of prophylaxis (i.e., as in adults,  $>100$  cells/mm<sup>3</sup> for children aged

≥ 6 years [**strong, high**]; and >200 cells/mm<sup>3</sup> for children aged 2 to <6 years [**strong, moderate**]).

On the basis of both randomized controlled trials and observational data, primary prophylaxis for MAC can be safely discontinued in adults with HIV infection who respond to ART with an increase in CD4 count.<sup>28,29</sup> In a prospective study that evaluated the incidence of OIs after discontinuation of OI prophylaxis in 63 children with HIV infection with CD4 percentages ≥20% for those aged >6 years and ≥25% for those aged 2 to 6 years, no MAC events were observed during ≥2 years of follow up.<sup>30</sup> No specific recommendations exist for discontinuing MAC prophylaxis in children with HIV infection who are aged <2 years.<sup>30</sup>

## Treatment

### III. In children with HIV infection and MAC disease, is testing MAC isolates for susceptibility indicated to guide management?

- Testing of MAC isolates for susceptibility to clarithromycin or azithromycin is recommended (**strong, very low**).

Retrospective cohort studies have shown macrolide resistance in initial sterile site isolates of MAC from patients with HIV infection.<sup>31</sup> Very small randomized control trials in adults have shown that only macrolide resistance correlates with clinical outcome, and therefore testing of MAC isolates for susceptibility to clarithromycin or azithromycin is recommended.<sup>32,33</sup>

### IV. In children with HIV infection and MAC disease, does combination therapy with either clarithromycin or azithromycin plus ethambutol, as opposed to monotherapy, prevent or delay the emergence of resistance?

- Combination therapy with a minimum of 2 drugs (e.g., either clarithromycin or azithromycin plus ethambutol) is recommended to prevent or delay the emergence of resistance (**strong, moderate**). Monotherapy is associated with the emergence of high-level drug resistance.

There is a lack of pediatric literature to guide the clinical management of children with HIV infection with disseminated MAC. Small retrospective studies confirm the incidence of MAC in severely immunosuppressed children.<sup>34,35</sup> Studies in adults showed that combination therapy of MAC with a minimum of 2 drugs prevented or delayed emergence of resistance.<sup>33,36-40</sup> In a study evaluating combination MAC therapy, there was no difference in relapse rates between treatment with the combination of clarithromycin and ethambutol or with both drugs plus rifabutin, suggesting that rifabutin did not provide any additional benefit.<sup>39</sup>

### V. In children with HIV infection and MAC disease, does the use of clarithromycin (as compared to azithromycin) improve clearance of bacteremia?

- There are insufficient data to recommend the use of clarithromycin over azithromycin. On the basis of a small randomized controlled trial in adults, which showed that the median time to clearance was shorter for clarithromycin than for azithromycin (4.4 versus >16 weeks) and that the organism was eliminated from the bloodstream in 86% of the patients in the clarithromycin group and in only 38% of those in the azithromycin group, some experts use clarithromycin as the preferred first agent. Azithromycin is reserved for patients with substantial intolerance to clarithromycin or when drug interactions with clarithromycin are a concern (**strong, low**).

### VI. In children with HIV infection and MAC disease who are treated with combination therapy, does the addition of a third agent provide improved clearance of infection?

- Use of rifabutin as a third drug added to the macrolide/ethambutol regimen is controversial (**weak, very low**).

Pediatric studies are lacking, but one randomized controlled open label study in adults compared clarithromycin plus ethambutol to clarithromycin plus rifabutin versus clarithromycin + ethambutol + rifabutin. While microbiologic response was similar, the 3-drug arm had improved mortality, as well as less relapse of infection.<sup>39</sup> There were no noted differences in the development of resistance in those who relapsed. On the basis of these studies, some experts would add rifabutin as a third drug to the clarithromycin plus ethambutol regimen, particularly in the absence of ART and in the presence of high mycobacterial counts. However, drug interactions should be checked carefully, and more intensive toxicity monitoring may be warranted with such combination therapy (**strong, very low**).<sup>19</sup>

Other experts recommend against using this third agent in children because of rifabutin's increased cytochrome P450 activity, which leads to increased clearance of other drugs such as PIs and NNRTIs, and the potential for increased toxicity associated with concomitant administration of drugs. Guidelines and recommendations exist for dose adjustments necessary in adults treated with rifabutin and PIs, but the absence of data in children precludes extrapolating these guidelines and recommendations to children with HIV undergoing treatment for disseminated MAC.

#### **VII. In patients with HIV with MAC infection who are antiretroviral naive, what is the optimal timing to start ART to prevent IRIS?**

- In patients with disseminated MAC disease who have not been treated previously with or are not receiving effective ART, initiation of ART generally should be withheld until after the first 2 weeks of antimycobacterial therapy have been completed to reduce the risk of drug interactions and complications associated with IRIS and to lower the pill burden. However, ART should be started as soon as possible after the first 2 weeks of initiating antimycobacterial therapy to reduce the risk of developing additional AIDS-defining OIs, and to facilitate immune reconstitution and further improve the response to antimycobacterial therapy (**weak, very low**). Children with moderate symptoms of IRIS can be treated symptomatically with nonsteroidal anti-inflammatory drugs (NSAIDs) or, if unresponsive to NSAIDs, a short course (such as 4 weeks) of systemic corticosteroid therapy while continuing to receive ART.

#### **VIII. In patients with HIV and MAC infection with treatment failure (defined as the absence of clinical response and the persistence of mycobacteremia after 8 to 12 weeks of treatment) is there an indication to repeat susceptibility testing to help guide clinical management?**

- Repeat susceptibility testing of MAC isolates is recommended in this situation, and a new multidrug regimen of two or more drugs not previously used, and to which the isolate is susceptible, should be administered (**strong, very low**). Drugs that should be considered for this scenario include rifabutin, amikacin, and a quinolone.

### **Secondary Prevention**

#### **IX. In children with HIV with disseminated MAC and continued immunosuppression, does secondary prophylaxis prevent recurrence of infection?**

- Children with a history of disseminated MAC and continued immunosuppression should receive lifelong prophylaxis to prevent recurrence (**strong, very low**). Secondary prophylaxis typically consists of continued multidrug therapy used in treatment of disease.

There are no pediatric data regarding secondary prophylaxis for MAC infection; however, low quality evidence from a randomized clinical trial in adults showed no difference in relapse rates in participants receiving the combination of clarithromycin, ethambutol, and rifabutin and in those receiving the combination of clarithromycin and ethambutol, but the 3-drug regimen showed a reduction in mortality.<sup>39</sup>

There remain concerns regarding toxicity and drug interactions with rifabutin. There are no data that look at azithromycin plus ethambutol for secondary prophylaxis. Prophylaxis in this setting means continuation of multidrug therapy, because use of a single agent (clarithromycin or azithromycin) for secondary prophylaxis carries a high risk of inducing drug-resistant MAC infection.

**X. In children with HIV with disseminated MAC and sustained CD4 recovery, is discontinuation of secondary prophylaxis associated with risk of relapse?**

- Some experts recommend discontinuation of therapy in children with HIV who meet **all** the following criteria:
  - Aged  $\geq 2$  years and have completed  $\geq 12$  months of treatment for MAC;
  - Remain asymptomatic for MAC;
  - Receiving stable ART (i.e., ART not requiring change for virologic or immunologic failure);
  - Have sustained ( $\geq 6$  months) CD4 count recovery well above the age-specific target for initiation of primary prophylaxis (i.e., as in adults,  $>100$  cells/mm<sup>3</sup> for children aged  $\geq 6$  years [**strong, low**], and  $>200$  cells/mm<sup>3</sup> for children aged 2 to  $<6$  years [**weak, very low**]).

There are no randomized clinical trials in children on discontinuation of secondary prophylaxis. On the basis of immune reconstitution data in adults<sup>41-44</sup> and data in children discontinuing primary prophylaxis<sup>30</sup>, some experts recommend discontinuation of secondary prophylaxis in children with HIV aged  $\geq 2$  years who have completed  $\geq 12$  months of treatment for MAC, remain asymptomatic for MAC, and are receiving stable ART (i.e., ART not requiring change for viral or immune failure) and who have sustained ( $\geq 6$  months) CD4 count recovery well above the age-specific target for initiation of primary prophylaxis (as in adults,  $>100$  cells/mm<sup>3</sup> for children aged  $\geq 6$  years [strong, low] and  $>200$  cells/mm<sup>3</sup> for children aged 2 to  $<6$  years [**weak, very low**]). Multidrug secondary prophylaxis should be reintroduced if the CD4 count falls below the age-related threshold.

**Dosing Recommendations for Prevention and Treatment of *Mycobacterium avium* Complex (MAC)**  
(page 1 of 2)

Preventive Regimen			
Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	<ul style="list-style-type: none"> <li>• Clarithromycin 7.5 mg/kg body weight (maximum 500 mg) orally twice daily, <i>or</i></li> <li>• Azithromycin 20 mg/kg body weight (maximum 1200 mg) orally once weekly</li> </ul>	<ul style="list-style-type: none"> <li>• Azithromycin 5 mg/kg body weight (maximum 250 mg) orally once daily</li> <li>• Children aged <math>&gt;5</math> years: rifabutin 300 mg orally once daily with food</li> </ul>	<p><u>Primary Prophylaxis Indicated for Children:</u></p> <ul style="list-style-type: none"> <li>• Aged <math>&lt;1</math> year: CD4 count <math>&lt;750</math> cells/mm<sup>3</sup>;</li> <li>• Aged 1 to <math>&lt;2</math> years: CD4 count <math>&lt;500</math> cells/mm<sup>3</sup>;</li> <li>• Aged 2 to <math>&lt;6</math> years: CD4 count <math>&lt;75</math> cells/mm<sup>3</sup>;</li> <li>• Aged <math>\geq 6</math> years: CD4 count <math>&lt;50</math> cells/mm<sup>3</sup></li> </ul> <p><u>Criteria for Discontinuing Primary Prophylaxis:</u></p> <ul style="list-style-type: none"> <li>• <b>Do not discontinue</b> in children aged <math>&lt;2</math> years.</li> <li>• After <math>\geq 6</math> months of ART, <i>and</i>:               <ul style="list-style-type: none"> <li>• Aged 2 to <math>&lt;6</math> years: CD4 count <math>&gt;200</math> cells/mm<sup>3</sup> for <math>&gt;3</math> consecutive months</li> <li>• Aged <math>\geq 6</math> years: CD4 count <math>&gt;100</math> cells/mm<sup>3</sup> for <math>&gt;3</math> consecutive months</li> </ul> </li> </ul> <p><u>Criteria for Restarting Primary Prophylaxis:</u></p> <ul style="list-style-type: none"> <li>• Aged 2 to <math>&lt;6</math> years: CD4 count <math>&lt;200</math> cells/mm<sup>3</sup></li> <li>• Aged <math>\geq 6</math> years: CD4 count <math>&lt;100</math> cells/mm<sup>3</sup></li> </ul>



**Dosing Recommendations for Prevention and Treatment of *Mycobacterium avium* Complex (MAC)**  
(page 2 of 2)

Preventive Regimen			
Indication	First Choice	Alternative	Comments/Special Issues
<b>Secondary Prophylaxis</b> (Chronic Suppressive Therapy)	<ul style="list-style-type: none"> <li>• Clarithromycin 7.5 mg/kg body weight (maximum 500 mg) orally twice daily, <b>plus</b></li> <li>• Ethambutol 15–25 mg/kg body weight (maximum 2.5 g) orally once daily, with or without food</li> <li>• Children aged &gt;5 years who received rifabutin as part of initial treatment: Rifabutin 5 mg/kg body weight (maximum 300 mg) orally once daily with food</li> </ul>	<ul style="list-style-type: none"> <li>• Azithromycin 5 mg/kg body weight (maximum 250 mg) orally once daily, <b>plus</b></li> <li>• Ethambutol 15–25 mg/kg body weight (maximum 2.5 g) orally once daily, with or without food</li> <li>• Children aged &gt;5 years who received rifabutin as part of initial treatment: Rifabutin 5 mg/kg body weight (maximum 300 mg) orally once daily with food</li> </ul>	<p><u>Secondary Prophylaxis Indicated:</u></p> <ul style="list-style-type: none"> <li>• Prior disease</li> </ul> <p><u>Criteria for Discontinuing Secondary Prophylaxis</u></p> <p><u>Fulfillment of All of the Following Criteria:</u></p> <ul style="list-style-type: none"> <li>• Completed ≥6 months of ART</li> <li>• Completed ≥12 months MAC therapy</li> <li>• Asymptomatic for signs and symptoms of MAC</li> <li>• Aged 2 to &lt;6 years: CD4 count &gt;200 cells/mm<sup>3</sup> for ≥6 consecutive months</li> <li>• Aged ≥6 years: CD4 count &gt;100 cells/mm<sup>3</sup> for ≥6 consecutive months</li> </ul> <p><u>Criteria for Restarting Secondary Prophylaxis:</u></p> <ul style="list-style-type: none"> <li>• Aged 2 to &lt;6 years: CD4 count &lt;200 cells/mm<sup>3</sup></li> <li>• Aged ≥6 years: CD4 count &lt;100 cells/mm<sup>3</sup></li> </ul>
<b>Treatment</b>	<p><u>Initial Treatment (≥2 Drugs):</u></p> <ul style="list-style-type: none"> <li>• Clarithromycin 7.5–15 mg/kg body weight (maximum 500 mg/dose) orally twice daily <b>plus</b> ethambutol 15–25 mg/kg body weight (maximum 2.5 g/day) orally once daily followed by chronic suppressive therapy</li> </ul> <p><u>For Severe Disease, Add:</u></p> <ul style="list-style-type: none"> <li>• Rifabutin 10–20 mg/kg body weight (maximum 300 mg/day) orally once daily</li> </ul>	<p><u>If Intolerant to Clarithromycin:</u></p> <ul style="list-style-type: none"> <li>• Azithromycin 10–12 mg/kg body weight (maximum 500 mg/day) orally once daily</li> </ul> <p><u>If Rifabutin Cannot Be Administered and a Third Drug is Needed in Addition to a Macrolide and Ethambutol, or if a Fourth Drug is Needed in Addition to Rifabutin for Patients with More Severe Symptoms or Disseminated Disease:</u></p> <ul style="list-style-type: none"> <li>• Ciprofloxacin 10–15 mg/kg orally twice daily (maximum 1.5 g/day), or</li> <li>• Levofloxacin 500 mg orally once daily, or</li> <li>• Amikacin 15–30 mg/kg body weight IV in 1 or 2 divided doses (maximum 1.5 g/day)</li> </ul>	<p>Combination therapy with a minimum of 2 drugs is recommended for ≥12 months.</p> <p>Clofazimine is associated with increased mortality in adults with HIV infection and should not be used.</p> <p>Children receiving ethambutol who are old enough to undergo routine eye testing should have monthly monitoring of visual acuity and color discrimination.</p> <p>Fluoroquinolones (e.g., ciprofloxacin and levofloxacin) are not labeled for use in children aged &lt;18 years because of concerns regarding potential effects on cartilage; use in children aged &lt;18 years requires an assessment of potential risks and benefits.</p> <p>Chronic suppressive therapy (secondary prophylaxis) is recommended in children and adults following initial therapy.</p>

Key to Acronyms: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; MAC = *Mycobacterium avium* complex; IV = intravenous

## References

1. Cassidy PM, Hedberg K, Saulson A, McNelly E, Winthrop KL. Nontuberculous mycobacterial disease prevalence and risk factors: a changing epidemiology. *Clin Infect Dis*. 2009;49(12):e124-129. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19911942>.
2. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med*. 2007;175(4):367-416. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17277290>.

3. Kasperbauer SH, Daley CL. Diagnosis and treatment of infections due to *mycobacterium avium* complex. *Semin Respir Crit Care Med*. 2008;29(5):569-576. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18810690>.
4. Vu TT, Daniel SJ, Quach C. Nontuberculous mycobacteria in children: a changing pattern. *J Otolaryngol*. 2005;34 Suppl 1:S40-44. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16089239>.
5. Chesney PJ. Nontuberculous mycobacteria. *Pediatr Rev*. 2002;23(9):300-309. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12205297>.
6. Gona P, Van Dyke RB, Williams PL, et al. Incidence of opportunistic and other infections in HIV-infected children in the HAART era. *JAMA*. 2006;296(3):292-300. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16849662>.
7. Nesheim SR, Kapogiannis BG, Soe MM, et al. Trends in opportunistic infections in the pre- and post-highly active antiretroviral therapy eras among HIV-infected children in the perinatal AIDS collaborative transmission study, 1986-2004. *Pediatrics*. 2007;120(1):100-109. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17606567>.
8. Perez Mato S, Van Dyke RB. Pulmonary infections in children with HIV infection. *Semin Respir Infect*. 2002;17(1):33-46. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11891517>.
9. Reed C, von Reyn CF, Chamblee S, et al. Environmental risk factors for infection with *mycobacterium avium* complex. *Am J Epidemiol*. 2006;164(1):32-40. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16675537>.
10. Peacock KH, Lewis L, Lavoie S. Erosive mediastinal lymphadenitis associated with *mycobacterium avium* infection in a pediatric acquired immunodeficiency syndrome patient. *Pediatr Infect Dis J*. 2000;19(6):576-578. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10877180>.
11. Hartmann P, Plum G. Immunological defense mechanisms in tuberculosis and MAC-infection. *Diagn Microbiol Infect Dis*. 1999;34(2):147-152. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10354865>.
12. Keller C, Kirkpatrick S, Lee K, Paul M, Hanson IC, Gilger M. Disseminated *mycobacterium avium* complex presenting as hematochezia in an infant with rapidly progressive acquired immunodeficiency syndrome. *Pediatr Infect Dis J*. 1996;15(8):713-715. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8858681>.
13. Kaplan JE, Benson C, Holmes KH, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the national institutes of health, and the HIV medicine association of the infectious diseases society of America. *MMWR Recomm Rep*. 2009;58(RR-4):1-207; quiz CE201-204. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19357635>.
14. Pacios E, Alcalá L, Ruiz-Serrano MJ, et al. Evaluation of bone marrow and blood cultures for the recovery of mycobacteria in the diagnosis of disseminated mycobacterial infections. *Clin Microbiol Infect*. 2004;10(8):734-737. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15301676>.
15. Shin SJ, Lee BS, Koh WJ, et al. Efficient differentiation of *mycobacterium avium* complex species and subspecies by use of five-target multiplex PCR. *J Clin Microbiol*. 2010;48(11):4057-4062. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20810779>.
16. Iamsawat S, Surawut S, Prammananan T, Leelaporn A, Jearanaisilavong J. Multiplex PCR for detection of clarithromycin resistance and simultaneous species identification of *mycobacterium avium* complex. *Southeast Asian J Trop Med Public Health*. 2010;41(3):590-601. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20578547>.
17. Luetkemeyer AF, Kendall MA, Wu X, et al. Evaluation of two line probe assays for rapid detection of *Mycobacterium tuberculosis*, tuberculosis (TB) drug resistance, and non-TB Mycobacteria in HIV-infected individuals with suspected TB. *J Clin Microbiol*. 2014;52(4):1052-1059. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24430455>.
18. Grosset J, Ji B. Prevention of the selection of clarithromycin-resistant *mycobacterium avium*-intracellulare complex. *Drugs*. 1997;54 Suppl 2:23-27; discussion 28-29. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9358197>.
19. Powderly WG. Treatment of infection due to *mycobacterium avium* complex. *Pediatr Infect Dis J*. 1999;18(5):468-469. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10353523>.

20. Smith JA, Mueller BU, Nussenblatt RB, Whitcup SM. Corneal endothelial deposits in children positive for human immunodeficiency virus receiving rifabutin prophylaxis for *mycobacterium avium* complex bacteremia. *Am J Ophthalmol*. 1999;127(2):164-169. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10030558>.
21. Lange CG, Woolley IJ, Brodt RH. Disseminated *mycobacterium avium*-intracellulare complex (MAC) infection in the era of effective antiretroviral therapy: is prophylaxis still indicated? *Drugs*. 2004;64(7):679-692. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15025543>.
22. American Academy of Pediatrics. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. American Academy of Pediatrics; 2015. Available at: <https://redbook.solutions.aap.org/DocumentLibrary/Red%20Book%202015%201.pdf>.
23. Race EM, Adelson-Mitty J, Kriegel GR, et al. Focal mycobacterial lymphadenitis following initiation of protease-inhibitor therapy in patients with advanced HIV-1 disease. *Lancet*. 1998;351(9098):252-255. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9457095>.
24. Phillips P, Chan K, Hogg R, et al. Azithromycin prophylaxis for *mycobacterium avium* complex during the era of highly active antiretroviral therapy: evaluation of a provincial program. *Clin Infect Dis*. 2002;34(3):371-378. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11774085>.
25. Steenhoff AP, Wood SM, Shah SS, Rutstein RM. Cutaneous *mycobacterium avium* complex infection as a manifestation of the immune reconstitution syndrome in a human immunodeficiency virus-infected child. *Pediatr Infect Dis J*. 2007;26(8):755-757. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17848894>.
26. Babiker ZO, Beeston C, Purcell J, Desai N, Ustianowski A. *Mycobacterium avium* complex suppurative parotitis in a patient with human immunodeficiency virus infection presenting with immune reconstitution inflammatory syndrome. *J Med Microbiol*. 2010;59(Pt 11):1365-1367. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20634331>.
27. Powderly WG. Prophylaxis for opportunistic infections in an era of effective antiretroviral therapy. *Clin Infect Dis*. 2000;31(2):597-601. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10987727>.
28. Currier JS, Williams PL, Koletar SL, et al. Discontinuation of *mycobacterium avium* complex prophylaxis in patients with antiretroviral therapy-induced increases in CD4+ cell count. A randomized, double-blind, placebo-controlled trial. AIDS clinical trials group 362 study team. *Ann Intern Med*. 2000;133(7):493-503. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11015162>.
29. Brooks JT, Song R, Hanson DL, et al. Discontinuation of primary prophylaxis against *mycobacterium avium* complex infection in HIV-infected persons receiving antiretroviral therapy: observations from a large national cohort in the United States, 1992-2002. *Clin Infect Dis*. 2005;41(4):549-553. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16028167>.
30. Nachman S, Gona P, Dankner W, et al. The rate of serious bacterial infections among HIV-infected children with immune reconstitution who have discontinued opportunistic infection prophylaxis. *Pediatrics*. 2005;115(4):e488-494. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15772172>.
31. Gardner EM, Burman WJ, DeGroot MA, et al. Conventional and molecular epidemiology of macrolide resistance among new *mycobacterium avium* complex isolates recovered from HIV-infected patients. *Clin Infect Dis*. 2005;41(7):1041-1044. Available at: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=16142672&query\\_hl=150&itool=pubmed\\_docsum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16142672&query_hl=150&itool=pubmed_docsum).
32. Sison JP, Yao Y, Kemper CA, et al. Treatment of *mycobacterium avium* complex infection: do the results of *in vitro* susceptibility tests predict therapeutic outcome in humans? *J Infect Dis*. 1996;173(3):677-683. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8627032>.
33. Chaisson RE, Benson CA, Dube MP, et al. Clarithromycin therapy for bacteremic *mycobacterium avium* complex disease. A randomized, double-blind, dose-ranging study in patients with AIDS. AIDS clinical trials group protocol 157 study team. *Ann Intern Med*. 1994;121(12):905-911. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7978715>.
34. Rutstein RM, Cobb P, McGowan KL, Pinto-Martin J, Starr SE. *Mycobacterium avium* intracellulare complex infection in HIV-infected children. *AIDS*. 1993;7(4):507-512. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8099487>.

35. Lewis LL, Butler KM, Husson RN, et al. Defining the population of human immunodeficiency virus-infected children at risk for *mycobacterium avium*-intracellulare infection. *J Pediatr*. 1992;121(5 Pt 1):677-683. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1432413>.
36. Cohn DL, Fisher EJ, Peng GT, et al. A prospective randomized trial of four three-drug regimens in the treatment of disseminated *mycobacterium avium* complex disease in AIDS patients: excess mortality associated with high-dose clarithromycin. Terry Beirn community programs for clinical research on AIDS. *Clin Infect Dis*. 1999;29(1):125-133. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10433575>.
37. Dunne M, Fessel J, Kumar P, et al. A randomized, double-blind trial comparing azithromycin and clarithromycin in the treatment of disseminated *mycobacterium avium* infection in patients with human immunodeficiency virus. *Clin Infect Dis*. 2000;31(5):1245-1252. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11073759>.
38. Benson CA, Williams PL, Cohn DL, et al. Clarithromycin or rifabutin alone or in combination for primary prophylaxis of *mycobacterium avium* complex disease in patients with AIDS: A randomized, double-blind, placebo-controlled trial. The AIDS clinical trials group 196/terry beirn community programs for clinical research on AIDS 009 protocol team. *J Infect Dis*. 2000;181(4):1289-1297. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10762562>.
39. Benson CA, Williams PL, Currier JS, et al. A prospective, randomized trial examining the efficacy and safety of clarithromycin in combination with ethambutol, rifabutin, or both for the treatment of disseminated *mycobacterium avium* complex disease in persons with acquired immunodeficiency syndrome. *Clin Infect Dis*. 2003;37(9):1234-1243. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14557969>.
40. Gordin FM, Sullam PM, Shafran SD, et al. A randomized, placebo-controlled study of rifabutin added to a regimen of clarithromycin and ethambutol for treatment of disseminated infection with *mycobacterium avium* complex. *Clin Infect Dis*. 1999;28(5):1080-1085. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10452638>.
41. Aberg JA, Williams PL, Liu T, Lederman HM, et al. A study of discontinuing maintenance therapy in human immunodeficiency virus-infected subjects with disseminated *mycobacterium avium* complex: AIDS clinical trial group 393 study team. *J Infect Dis*. 2003;187:1046-52. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12660918>.
42. Zeller V, Truffot C, Agher R, et al. Discontinuation of secondary prophylaxis against disseminated *mycobacterium avium* complex infection and toxoplasmic encephalitis. *Clin Infect Dis*. 2002;34(5):662-667. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11810599>.
43. Kirk O, Reiss P, Uberti-Foppa C, et al. Safe interruption of maintenance therapy against previous infection with four common HIV-associated opportunistic pathogens during potent antiretroviral therapy. *Ann Intern Med*. 2002;137(4):239-250. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12186514>.
44. Shafran SD, Mashinter LD, Phillips P, et al. Successful discontinuation of therapy for disseminated *mycobacterium avium* complex infection after effective antiretroviral therapy. *Ann Intern Med*. 2002;137(9):734-737. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12416943>.