Mycobacterium avium Complex Disease

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Panel's Recommendations

Primary Prevention of *Mycobacterium avium* Complex (MAC)

- Prophylaxis with either clarithromycin or azithromycin should be offered to children with HIV who have advanced immunosuppression, as defined by CD4 T lymphocyte (CD4) cell count below, and who are not on a fully suppressive antiretroviral (ARV) regimen (AIII). Disseminated MAC should be excluded prior to initiating prophylaxis.
  - *Children Aged <1 Year:* <750 cells/mm^3
  - *Children Aged 1–5 Years:* <500 cells/mm^3
  - *Children Aged ≥6 Years:* <200 cells/mm^3
- For children who cannot tolerate azithromycin or clarithromycin, rifabutin may be used despite concerns of drug interactions and lack of efficacy data in children (BIII).

Discontinuing Primary Prophylaxis

- Primary prophylaxis cannot be discontinued in children with HIV aged <2 years and should be discontinued in children with HIV ≥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 (AI*).

Treatment of MAC in Children With HIV

- Testing of all MAC isolates for susceptibility to clarithromycin or azithromycin, in addition to amikacin, linezolid, and moxifloxacin, is recommended (AIII).
- Combination therapy with a minimum of two drugs for ≥12 months (e.g., clarithromycin or azithromycin plus ethambutol) is recommended to prevent or delay the emergence of resistance (AIII). Monotherapy is associated with the emergence of high-level drug resistance.
- Clarithromycin is suggested as the preferred macrolide, although azithromycin is preferred by many experts because of better tolerance and fewer drug interactions (BIII).
- Some experts would add rifabutin as a third drug to the macrolide/ethambutol regimen (CIII), particularly in the absence of suppressive ART and in the presence of severe illness; however, with such combination therapy, drug interactions should be checked carefully, and more intensive toxicity monitoring may be warranted (AIII). Ritonavir may increase the concentration of rifabutin and its active metabolite(s). Other experts recommend against the use of rifabutin as a third agent in children due to 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.
- In children with HIV and disseminated MAC disease who have no prior ART experience or are not receiving effective ART, ART should be started at the same time as antimycobacterial therapy (BII*). The regimens should be modified when there is potential for an adverse drug–drug interaction(s) between the ARV and antimycobacterial drugs (BII*).

Management of Treatment Failure

- Children who fail to respond clinically and have persistent mycobacteremia after 8–12 weeks of treatment should undergo repeat susceptibility testing of MAC isolates and should subsequently start a new multidrug regimen involving at least two drugs not previously used and to which the isolate is susceptible (AIII). Drugs that should be considered for this scenario include rifabutin (if not previously used), amikacin, ciprofloxacin, moxifloxacin, and/or bedaquiline (age 5 and older and at least 15 kg).

Secondary Prophylaxis

- Children with a history of disseminated MAC and continued immunosuppression should receive lifelong prophylaxis to prevent recurrence (AIII). Secondary prophylaxis typically consists of continued multidrug therapy used in the treatment of disease.
- Some experts recommend discontinuation of therapy in children with HIV who meet all the following criteria:
  - Aged ≥2 years and have completed ≥12 months of treatment for MAC; *and*
  - Remain asymptomatic for MAC; *and*
  - Receiving stable ART (i.e., ART not requiring change for virologic or immunologic failure); *and*
  - Have sustained (≥6 months) CD4 count recovery well above the age-specific target for initiation of primary prophylaxis (i.e., as in adults, >100 cells/mm^3 for children aged ≥6 years [AII] and >200 cells/mm^3 for children aged 2 to <6 years [CII]).
- There are limited data to recommend discontinuation of secondary prophylaxis in children <2 years. However, if continuation of secondary prophylaxis for MAC is complicating ART compliance, discontinuation of MAC prophylaxis may be appropriate (CIII).

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

*Rating of Evidence: I = One or more randomized trials **in children**† 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**† 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**† 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**† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion*

†Studies that include children or children/adolescents, but not studies limited to postpubertal adolescents

Epidemiology

Current molecular technologies have led to the identification of more than 200 species within the *Mycobacterium* genus. *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 and are not typically distinguished in the microbiology laboratory. Surveillance data continue to show an increasing rate of MAC infection in some regions within the United States, particularly among women and people aged 65 years or older.[1] Comprehensive updated guidelines on the treatment of nontuberculous mycobacterial diseases were published in 2020.[2] In the United States, NTM infections outnumber *Mycobacterium tuberculosis* infections and have become an important cause of pulmonary morbidity in adults.[3] In children not infected with HIV, it appears that the overall prevalence of NTM is increasing over time.[4,5] However, disseminated NTM is rare in immunocompetent children. The incidence of all opportunistic infections has decreased since the advent of effective ARTs, and prevalence remains significantly lower than the pre-ART era.[6]

Before the advent of ART, MAC was second only to *Pneumocystis jirovecii* pneumonia among opportunistic infections (OIs) in children with HIV in the United States. With the availability of ART, all OIs have continued to decrease in children with HIV.[7] The incidence of MAC has greatly decreased, from 1.8 episodes per 100 person-years in the pre-ART era to 0.14 per 100 person-years in the ART era.[8,9] MAC is ubiquitous in the environment and presumably is acquired by routine exposures through inhalation, ingestion, or inoculation.[10]

MAC can appear as isolated lymphadenitis in children with and without HIV. In children with HIV, disseminated MAC 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 children under the age of five with HIV than in older children or adults with HIV. MAC is a recognized complication of advanced immunologic deterioration among children with HIV.[9-11]

Clinical Manifestations

Respiratory symptoms are uncommon in children with HIV 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. Gastrointestinal symptoms can occur alone or in combination with systemic findings, including lymphadenopathy, hepatomegaly, and splenomegaly. 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.[12]

Diagnosis

Procedures used to diagnose MAC in children with HIV are the same as those used for adults with HIV. 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). Isolation of MAC from a cervical lymph node but with no evidence of dissemination (negative blood cultures) indicates infection without dissemination. Blood cultures are a sensitive and minimally invasive technique for diagnosing disseminated MAC, with >90% of diagnosed individuals recording positive blood cultures.[12,13] 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. General guidelines for blood volume are 1 mL for infants and 1 mL per year of age up to the adult volume of 10 mL. The 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. MAC isolates can also be rapidly identified by their mycolic acid patterns from the same samples by high-performance liquid chromatography, line probe assays, and 16s rRNA gene sequencing. Single and multigene sequencing and matrix-assisted laser desorption ionization-time of flight mass spectrometry can also be used, although these techniques have differing ability to discriminate between species and subspecies and have variable costs. These diagnostic techniques may only be available at high-volume laboratories.[13-17]

Histology demonstrating macrophage-containing acid-fast bacilli is strongly indicative of MAC infection in children with typical signs and symptoms, but culture is essential to (1) differentiate NTM from *M. tuberculosis*; (2) determine which NTM is causing infection, and (3) perform drug-susceptibility testing. Testing of MAC isolates for susceptibility to clarithromycin or azithromycin is most useful because clinical response is correlated with macrolide susceptibility. 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.[13-17]

Although detection of MAC in stool or the respiratory tract may precede disseminated disease, no data demonstrates a correlation between initiation of prophylaxis in people with detectable organisms at these sites and reduced risk of developing disseminated MAC. Therefore, there is no recommendation for routine testing of stool or respiratory specimens for the presence of MAC.

Prevention Recommendations

Preventing Exposure

MAC is ubiquitous in the environment. Available information does not support specific recommendations regarding exposure avoidance.[1,17] Person-to-person transmission is not believed to occur for MAC.

Preventing First Episode of Disease

The most effective way to prevent disseminated MAC in children with HIV is to preserve immune function through the use of effective ART. With the advent of suppressive ART, few children require primary prophylaxis. Current recommendations in adults with advanced immunosuppression do not recommend primary prevention if ARVs are started unless the individual remains viremic and a fully suppressive regimen is not available (see Disseminated *Mycobacterium avium* Complex Disease in the Adult and Adolescent Opportunistic Infection Guidelines). Children with HIV who have advanced immunosuppression should be offered prophylaxis against disseminated MAC disease according to the CD4 count thresholds for children who remain viremic on ART but have no options for a fully suppressive ART regimen **(AIII).** Before prophylaxis is initiated in at-risk children, disseminated MAC disease must be ruled out, which includes obtaining a blood culture for MAC **(AIII).**

Published data defining CD4 values below which primary prophylaxis should be initiated were developed before the era of effective ART and typically used CD4 percentages rather than absolute values. However, CD4 absolute values were published in 2014; these values were used to define immunosuppression in children with HIV by age and may be used to guide MAC prophylaxis.[18]

Prophylaxis with either clarithromycin or azithromycin should be offered to children with HIV who have advanced immunosuppression based on the CD4 thresholds below **(AIII).**

- *Children Aged <1 Year:* <750 cells/mm^3
- *Children Aged 1 to 5 Years:* <500 cells/mm^3
- *Children Aged ≥6 Years:* <200 cells/mm^3

Based on randomized controlled trials, clarithromycin and azithromycin are the preferred prophylactic agents for adults with HIV.[19-21] Although there are no randomized controlled trials in children, either clarithromycin and azithromycin is recommended for prophylaxis in children **(AIII);** 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 **(AIII).** 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 **(BIII).**

Based on both randomized controlled trials and observational data in adults with HIV, primary prophylaxis for MAC can be safely discontinued in children with HIV who respond to ART with an increase in CD4 count.[22,23] In a prospective study that evaluated the incidence of OIs after discontinuation of OI prophylaxis in 63 children with HIV with CD4 percentages ≥20% for those aged >6 years and ≥25% for those aged 2 to 6 years, no MAC events were observed at a median of 2 years of follow-up.[23]

Primary prophylaxis cannot be discontinued in children aged <2 years **(BIII)** but should be discontinued in children with HIV aged ≥2 years receiving stable ART for ≥6 months and experiencing sustained (>3 months) CD4 count recovery well above the age-specific target for initiation of prophylaxis **(AI*).**

Treatment Recommendations

Treating Disease

Disseminated MAC infection should be treated in consultation with a pediatric infectious disease specialist who has expertise in pediatric HIV.

In the United States, treatment with ART has become the standard practice for all children with HIV. The optimal time to start ART in previously untreated children who present with disseminated MAC is unknown, but recovery of the immune system is critical in controlling disseminated MAC. In such children, ART should generally be initiated at the same time as treatment for MAC. The regimens should be modified when there is potential for an adverse drug–drug interaction(s) between the antiretroviral and antimycobacterial drugs **(AIII).**

While waiting for identification and susceptibility results from diagnostic specimens, as well as immune system recovery, many experts will start an initial regimen of more than three drugs that are likely to be active against a broad range of mycobacteria (i.e., both *M. tuberculosis* and NTM), including ethambutol, azithromycin, and rifabutin, plus a fluoroquinolone and/or potentially an injectable aminoglycoside (e.g., amikacin). When specifically treating disseminated MAC, combination therapy with at least two active drugs (typically a macrolide plus ethambutol) and improving immunologic status with effective ART are cornerstones for controlling disseminated MAC disease.

Macrolide monotherapy results in emergence of high-level drug resistance within weeks.[24] Clarithromycin levels can be increased by protease inhibitors (PI) and decreased by the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz, but no data are available to recommend dose adjustments for children. Azithromycin is generally preferred over clarithromycin because it is not metabolized as significantly by the cytochrome P450 (CYP) system; therefore, azithromycin can be used without major concern for significant drug interactions with PIs and NNRTIs. However, it is important to always perform a drug–drug interaction check and/or consult with a pharmacist.

There are no definitive data demonstrating improved survival after adding rifabutin to the typical macrolide plus ethambutol regimen.[25] However, this regimen may be considered in select pediatric patients with severe immunosuppression and widely disseminated MAC. Rifabutin is both a substrate and inducer of CYP3A4, which may lead to increased levels of nonboosted and boosted PIs.[25] This may warrant increased monitoring for drug toxicity when rifabutin and PIs are used together. Rifabutin should not be used with select integrase strand transfer inhibitors (INSTIs) because of a

significant reduction in therapeutic levels of these agents: bictegravir, once-daily elvitegravir, and injectable cabotegravir.[26] The INSTIs raltegravir, dolutegravir, and oral cabotegravir may be used without dose adjustment. Careful monitoring for appropriate response to ARV therapy and toxicity is important when using a rifabutin-containing regimen.

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 from a small unpublished study of 22 children with HIV (median age: 9 years) who received rifabutin in combination with two or more other antimycobacterial drugs for the treatment of MAC for 1 to 183 weeks were used by the U.S. Food and Drug Administration to create the product label; mean rifabutin doses ranged from 18.5 mg/kg for infants to 8.6 mg/kg for children aged 2 to 10 years, and reported adverse effects were similar to those reported in adults.[26] The most commonly reported dose in children has been rifabutin 5 mg/kg. Therapy is typically prolonged and depends upon response and immune reconstitution. Whether treatment success differs between rifampin versus rifabutin is unclear, although drug–drug interactions may be less significant with rifabutin.[27,28]

Testing of MAC isolates for susceptibility to clarithromycin or azithromycin, in addition to amikacin, moxifloxacin, and linezolid, is recommended **(AIII).**

Clarithromycin is recommended as the preferred macrolide, although azithromycin can be used as an alternative for children with substantial intolerance to clarithromycin or when drug interactions with clarithromycin are a concern **(BIII).**

Use of rifabutin as a third drug added to the macrolide plus ethambutol regimen is controversial **(CIII).** Pediatric studies are lacking, but one randomized controlled open-label study in adults compared clarithromycin plus ethambutol to clarithromycin plus rifabutin versus clarithromycin plus ethambutol plus rifabutin. Although the microbiologic response was similar, the three-drug arm had reduced macrolide resistance when relapse occurred.[33] Based on 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 severe illness. However, drug interactions should be checked carefully, and more intensive toxicity monitoring may be warranted with such combination therapy **(AIII).** Other experts recommend against using rifabutin as a third agent in children due to increased CYP450 activity. Guidelines and recommendations exist for dose adjustments necessary in adults treated with rifabutin and some components of ART regimens, but the absence of data in children precludes extrapolating these guidelines and recommendations to children with HIV undergoing treatment for disseminated MAC.[29] Pharmacokinetic data are available on the use of rifabutin with the boosted PI lopinavir/ritonavir in children with HIV/tuberculosis coinfection, which may be useful if rifabutin is considered.[29] Newer anti-mycobacterial agents, such as bedaquiline, have been used in adults for treatment of NTMs, but there are no data on use in children.[37]

Monitoring and Adverse Events

Clinically, most patients improve substantially during the first 4 to 6 weeks of therapy. Some experts would consider a repeat blood culture after 4 to 6 weeks of therapy for all children with an initial positive culture, regardless of clinical response to therapy. Fever improvement can be expected within 2 to 4 weeks after initiation of appropriate therapy. However, for those with more extensive disease, advanced immunosuppression, or failure to respond to ARV drugs, 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. Prolonged high-dose use of macrolides has been associated with hearing loss; however, there are no specific recommendations for routine hearing screening.[30] 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 relatively rare at doses of 15 mg/kg to 25 mg/kg in children with normal renal function. All children who are old enough to cooperate should undergo vision assessment prior to starting ethambutol and periodically during treatment. The risks and benefits of using ethambutol in very young children whose visual acuity cannot be monitored must be carefully considered.[31]

Children receiving clarithromycin plus rifabutin should be observed for rifabutin-related development of leukopenia, uveitis, polyarthralgia, and pseudojaundice. Tiny, almost transparent, asymptomatic peripheral and central corneal deposits that do not impair vision have been observed in some children with HIV receiving rifabutin.[27]

Immune reconstitution inflammatory syndrome (IRIS) has been reported in adults and children with HIV receiving MAC therapy and ART.[32-35] 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 has occurred after initiating ART (unmasking IRIS). In addition, paradoxical worsening of systemic or local MAC symptoms may occur as the immune system is rapidly reconstituted. Mycobacteremia is typically absent. Children with moderate symptoms of IRIS can be treated symptomatically with nonsteroidal anti-inflammatory drugs (NSAIDs) or, if unresponsive to NSAIDs, a short course (e.g., 4 weeks) of systemic corticosteroid therapy while continuing ART.

Managing Treatment Failure

Children who do not respond to therapy and either exhibit persistent symptoms or fail to record negative cultures are likely exhibiting 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 the event of MAC treatment failure. A new multidrug regimen adding two or more drugs not previously used and to which the isolate is susceptible should be administered **(AIII).** Macrolides remain the most effective agent for MAC and should be continued if the isolate remains susceptible. Drugs that should be considered for this scenario include rifabutin (if not already used), amikacin, linezolid, ciprofloxacin or moxifloxacin, and/or bedaquiline (age ≥5). [12,17]

Preventing Recurrence

There are no pediatric data regarding secondary prophylaxis for MAC infection. However, children with a history of disseminated MAC and continued immunosuppression should receive lifelong prophylaxis to prevent recurrence **(CIII).** Many experts recommend clarithromycin plus ethambutol for secondary prophylaxis. Monotherapy with clarithromycin or azithromycin is associated with the development of high-level drug resistance.

Discontinuing Secondary Prophylaxis

In the era of combination ART, very few cases of invasive MAC have been reported, and recommendations for the discontinuation of secondary prophylaxis remain unchanged. On the basis of immune reconstitution data in adults[31,36] and data in children discontinuing primary prophylaxis, secondary prophylaxis should be discontinued in children with HIV who are aged ≥2 years and have completed ≥6 months of treatment for MAC, remain asymptomatic for MAC, are receiving stable ART (i.e., ART not requiring change for virologic or immune failure), and who have sustained (≥6 months) CD4 count recovery well above the age-specific targets for initiation of primary prophylaxis (i.e., as in adults, >100 cells/mm^3 for children aged ≥6 years **[AII]** and >200 cells/mm^3 for children aged 2 years to <6 years **[BII]**). Multidrug secondary prophylaxis should be reintroduced if the CD4 count falls below the age-related threshold.

There are no data and limited clinical experience to guide the decision to discontinue secondary prophylaxis for children aged <2 years who have completed 1 year of treatment for disseminated MAC and who are receiving effective ART. However, if continuation of secondary prophylaxis for MAC is complicating ART compliance, discontinuation of MAC prophylaxis may be appropriate **(CIII).** Consultation with a pediatric HIV expert is advised.

Dosing Recommendations for Prevention and Treatment of *Mycobacterium avium* Complex

Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	• Clarithromycin[a] 7.5 mg/kg (maximum 500 mg/dose) PO twice daily, *or* • Azithromycin 20 mg/kg (maximum 1,200 mg) PO once weekly	• Azithromycin 5 mg/kg (maximum 250 mg) PO once daily • For children who cannot tolerate azithromycin or clarithromycin, rifabutin (5 mg/kg/daily, maximum dose 300 mg) is an alternative prophylactic agent for MAC, although drug interactions and a lack of efficacy data in children limit its use.	Primary Prophylaxis Indicated for Children With HIV Who Have Advanced Immunosuppression, as Defined by CD4 Count Below, and Who Are Not on a Fully Suppressive ARV Regimen • *Aged <1 Year:* CD4 count <750 cells/mm^3 • *Aged 1 to 5 Years:* CD4 count <500 cells/mm^3 • *Aged ≥6 Years:* CD4 count <200 cells/mm^3 Criteria for Discontinuing Primary Prophylaxis • Do not discontinue in children aged <2 years. • After ≥6 months of ART, *and* o *Aged 2 to <6 Years:* CD4 count >200 cells/mm^3 for >3 consecutive months o *Aged ≥6 Years:* CD4 count >100 cells/mm^3 for >3 consecutive months

Indication	First Choice	Alternative	Comments/Special Issues
			Criteria for Restarting Primary Prophylaxis • *Aged 2 to <6 Years:* CD4 count ≤200 cells/mm^3 • *Aged ≥6 Years:* CD4 count ≤100 cells/mm^3
Secondary Prophylaxis (Chronic Suppressive Therapy)	• See initial treatment below. • *For Children Aged ≥6 Years Who Received Rifabutin as Part of Initial Treatment:* rifabutin[a] 5 mg/kg (maximum 300 mg) PO once daily with food	• Azithromycin 5 mg/kg (maximum 250 mg) PO once daily, *plus* • Ethambutol 15–25 mg/kg (maximum 2.5 g) PO once daily, with or without food • Children aged ≥6 years who received rifabutin as part of initial treatment: rifabutin 5 mg/kg (maximum 300 mg) PO once daily with food	Secondary Prophylaxis Indicated • Prior disease Criteria for Discontinuing Secondary Prophylaxis • Children with a history of disseminated MAC and continued immunosuppression should receive lifelong prophylaxis to prevent recurrence. • There are limited data to recommend discontinuation of secondary prophylaxis in children aged <2 years. However, if continuation of secondary prophylaxis for MAC is complicating ART compliance, discontinuation of MAC prophylaxis may be appropriate. *Fulfillment of All of the Following Criteria* • Completed ≥6 months of stable ART, *and* • Completed ≥12 months of MAC therapy, *and* • Asymptomatic for signs and symptoms of MAC, *and either* • *Aged 2 to <6 Years:* CD4 count >200 cells/mm^3 for ≥6 consecutive months, *or* • *Aged ≥6 Years:* CD4 count >100 cells/mm^3 for ≥6 consecutive months Criteria for Restarting Secondary Prophylaxis • *Aged 2 to <6 Years:* CD4 count ≤200 cells/mm^3 • *Aged ≥6 Years:* CD4 count ≤100 cells/mm^3

Indication	First Choice	Alternative	Comments/Special Issues
Treatment	Initial Treatment (≥2 Drugs): • Clarithromycin[a] 7.5–15 mg/kg (maximum 500 mg/dose) PO twice daily, *plus* • Ethambutol 15–25 mg/kg (maximum 2.5 g/day) PO once daily followed by chronic suppressive therapy *If Experiencing Severe Disease (Extensive End Organ Involvement, Prolonged Symptoms, Slow Response to Therapy)* • Add rifabutin[a] 10–20 mg/kg (maximum 300 mg/day) PO once daily	If Intolerant to Clarithromycin • Azithromycin 10–12 mg/kg (maximum 500 mg/day) PO once daily, plus ethambutol For Children With Severe Symptoms or Disseminated Disease Who Need a Rifabutin Alternative or a Fourth Drug to Supplement a Macrolide/ Ethambutol/Rifabutin Regimen • Amikacin[b] 15–30 mg/kg (maximum 1.5 g/day) IV in one or two divided doses. Therapeutic drug monitoring (peak and trough levels) is required, *or* • Linezolid 10 mg/kg/dose PO every 8 hours for age 1 month to <12 years (maximum 600 mg/dose) and 10 mg/kg/dose PO every 12 hours (maximum 600 mg) for age ≥12 years, *or* • Moxifloxacin 7.5–10 mg/kg (maximum dose 400 mg daily) PO once daily, *or* • Levolfoxacin 15-20 mg/kg/dose PO once daily (maximum dose 750 mg), *or* • Ciprofloxacin 10–15 mg/kg (maximum 1.5 g/day) PO twice daily, *or* • Bedaquiline for children aged ≥5 years weighing ≥15 kg (based on MDR-TB regimens): o *Weeks 1–2:* 400 mg once daily o *Weeks 3–24:* 200 mg three times weekly o For therapy beyond 24 weeks, consider consultation with a pediatric infectious disease/HIV expert.	Susceptibility testing is recommended prior to treatment initiation. Combination therapy with a minimum of two drugs is recommended for ≥12 months. Careful monitoring for drug–drug interactions is advised. Clofazimine is associated with increased mortality in adults with HIV and should not be used. Children receiving ethambutol who are old enough to undergo routine eye testing should have monthly monitoring of visual acuity and color discrimination. Fluoroquinolones (e.g., ciprofloxacin and moxifloxacin) are used with caution in children aged <18 years because of concerns regarding potential effects on cartilage; use in children aged <18 years requires an assessment of potential risks and benefits. Chronic suppressive therapy (secondary prophylaxis) is recommended in children and adults following initial therapy. Limited data for bedaquiline in adults with NTM.

Key: ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; IV = intravenous; MAC = *Mycobacterium avium* complex; MDR-TB = multidrug-resistant tuberculosis; NTM = nontuberculous mycobacteria; PO = orally

[a] Careful monitoring of drug–drug interactions is critical when using rifabutin or clarithromycin in children on ARVs.

[b] Amikacin levels for therapeutic drug monitoring: peak (C_{max}) 30–40 mg/L and trough (C_{min}) <5 mg/L for once daily dosing; C_{max} 65–80 mg/L for thrice weekly dosing

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