Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Mycobacterium avium complex and *Mycobacterium kansasii*. In: British HIV Association and British Infection Association guidelines for the treatment of opportunistic infection in HIV-seropositive individuals 2011.

Bibliographic Source(s)

Fisher M, Ong E, Pozniak A. Mycobacterium avium complex and Mycobacterium kansasii. In: British HIV Association and British Infection Association guidelines for the treatment of opportunistic infection in HIV-seropositive individuals 2011. HIV Med. 2011 Sep;12(Suppl 2):75-82. [63 references]

Guideline Status

This is the current release of the guideline.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- May 12, 2016 – Fluoroquinolone Antibacterial Drugs: The U.S. Food and Drug Administration (FDA) is advising that the serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with sinusitis, bronchitis, and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options.

Recommendations

Major Recommendations

Level of evidence (I–IV) ratings are defined at the end of the "Major Recommendations" field.

Mycobacterium avium Complex (MAC)

Diagnosis

- Diagnosis of disseminated *Mycobacterium avium* complex (DMAC) requires culture in blood or from a bone marrow aspirate or fluid from a normally sterile site or biopsy specimen (III).
- Culture of MAC from sputum or stool in the absence of other proof of DMAC is insufficient diagnostic evidence (III).

Treatment

Treatment Regimens for DMAC

- Antimycobacterial treatment of DMAC requires combination therapy that should include a macrolide and ethambutol, with or without rifabutin (Ib).
- Addition of rifabutin should be considered in cases with advanced immunosuppression, marked symptoms or an inability to construct an effective highly active antiretroviral therapy (HAART) regimen (III).
- Treatment failure is usually addressed with a combination of at least 2 new drugs including fluoroquinolones, amikacin and other agents (III).
- Treatment should be continued until there is an adequate immunological response to HAART or in the absence of this life-long (III).

Length of Treatment for DMAC

- Individuals receiving HAART with a virological response and a CD4 count >100 cells/µL for at least 3 months in whom there has been a clinical response to DMAC therapy for at least 3 months can discontinue therapy (III).
- Most studies of the treatment of DMAC were performed in the pre-HAART era. However, there is no doubt that one of the most effective treatments for DMAC is HAART. HAART should be initiated simultaneously or within 1 to 2 weeks of initiation of antimycobacterial therapy for DMAC disease, based on the experience with a range of opportunistic infections including a small number of cases with MAC (Zolopa et al., 2009) (IV).

Treatment Failure for DMAC

- Patients are considered to have treatment failure if there is no clinical response and mycobacteria are isolated from cultures after 4 to 8 weeks of MAC treatment to which the patient has been adherent. Drug susceptibility testing is of limited use for agents other than macrolides (III).
- A new combination of at least 2 drugs not previously used and to which the isolate should be susceptible should be constructed (III) – e.g., rifabutin (if not used previously), ciprofloxacin, levofloxacin, ofloxacin or moxifloxacin (Dubé et al., 1999), linezolid or amikacin.
- Other second-line agents (such as ethionamide, prothionamide or cycloserine) have been used anecdotally. Many clinicians would continue ethambutol since it facilitates the penetration of other agents into mycobacteria (IV).

Primary Prophylaxis

- Prophylaxis for DMAC with azithromycin 1250 mg weekly can be considered for individuals with CD4 counts <50 cells/µL (Ib).
- Primary prophylaxis can be stopped in the presence of a virological response to HAART (viral load <50 copies per mL) and a CD4 count >50 cells/µL for at least 3 months (III).
- Lowering the CD4 count at which primary prophylaxis should be considered to <50 cells/µL is recommended in line with many other guidelines. It is therefore recommended that MAC prophylaxis *should* be considered for individuals with a CD4 count of <50 cells/µL who are either not accepting HAART or who are experiencing HAART failure (Ib).
- In such individuals, the decision to recommend MAC prophylaxis will need to balance the potential clinical benefits against the additional pill burden, possible added drug-related toxicity, and risk of resistance if undiagnosed DMAC is present (IV).

Impact of HAART

- HAART should be commenced within 2 weeks of starting MAC therapy (IV).
- There are currently no randomized data to recommend the optimal management strategy for MAC immune reconstitution inflammatory syndrome (IRIS). However, the following have been used with anecdotal benefit (III) and may be considered in select cases:
    1. Corticosteroid therapy, with 20–40 mg of oral prednisolone a day for 4 to 8 weeks has been most frequently used.
    2. Interleukin-2 (IL-2) and granulocyte-macrophage colony-stimulating factor (GM-CSF) have been used successfully in a small number of patients (Pires et al., 2005).
    3. Leukotriene inhibitors have been used in tuberculosis (TB)-associated IRIS in cases refractory/intolerant to steroids (Lipman & Carding, 2007; Hardwick et al., 2006).
    4. Repeated fine-gauge needle aspiration of pus, as used with lymphadenitis due to *Mycobacterium tuberculosis*.

Mycobacterium kansasii

Diagnosis

- Since *M. kansasii* may be a commensal organism, diagnosis requires both repeated isolation and a compatible clinical and radiological picture (IV).

Treatment

- Where clinically indicated, treatment is with rifamycin + ethambutol + isoniazid for a minimum of 12 months (IV).
- Therapy should be with a rifamycin such as rifampicin 600 mg once daily (od) or rifabutin 300 mg od plus ethambutol 15 mg/kg with high-dose isoniazid 300 mg od plus pyridoxine 20 mg od for at least 12 months (IV) and possibly for at least 12 months of documented sputum negativity. However, the duration is based on pre-HAART and/or human immunodeficiency virus (HIV)-seronegative extrapolation data (Griffith et al., 2007). There is also experience with the combination of clarithromycin, rifampicin and ethambutol (IV).

Definitions:

Level of Evidence

Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well designed controlled study without randomization
IIb	Evidence obtained from at least one other type of well designed quasi-experimental study
III	Evidence obtained from well designed non-experimental descriptive studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

- Atypical *Mycobacterium* infections
  - *Mycobacterium avium* complex infection
  - *Mycobacterium kansasii infection*
- Human immunodeficiency virus (HIV) seropositivity

Guideline Category

Diagnosis

Management

Prevention

Treatment

Clinical Specialty

Infectious Diseases

Internal Medicine

Pathology

Preventive Medicine

Radiology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To help physicians in the United Kingdom investigate and manage human immunodeficiency virus (HIV)-seropositive patients suspected of or having *Mycobacterium avium* complex and/or *Mycobacterium kansasii* infections

Target Population

Human immunodeficiency virus (HIV)-seropositive patients suspected of or having *Mycobacterium avium* complex and/or *Mycobacterium kansasii* infections

Interventions and Practices Considered

Diagnosis

1. Disseminated *Mycobacterium avium* complex (DMAC) infection
    - Culture in blood or from a bone marrow aspirate or fluid from a normally sterile site or biopsy specimen
    - Culture of sputum or stool, with other proof
2. *Mycobacterium kansasii* infection
    - Repeated isolation
    - Compatible clinical and radiological picture

Treatment/Prevention

1. DMAC infection
    - Combination therapy of a macrolide (clarithromycin or azithromycin) and ethambutol, with or without rifabutin
    - Combination of at least two new drugs including fluoroquinolones, amikacin and other agents (for treatment failure)
    - Continuation of therapy until there is an adequate response to highly active antiretroviral therapy (HAART)
    - Second-line agents for treatment failure
    - Prophylaxis with azithromycin
    - Therapy for MAC immune reconstitution inflammatory syndrome (IRIS): corticosteroids, interleukin-2 (IL-2), granulocyte-macrophage colony-stimulating factor (GM-CSF), leukotriene inhibitors
    - Timing of initiation of HAART
2. *Mycobacterium kansasii* infection
    - Rifamycin + ethambutol + isoniazid
    - Primary prophylaxis (not recommended)

Major Outcomes Considered

- Sensitivity and specificity of diagnostic tests
- Emergence of drug resistance
- Incidence of disseminated *Mycobacterium avium* complex (DMAC) infections
- Relapse rate
- Response rate
- Morbidity and mortality
- Adverse events and drug interactions

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The PubMed database was searched under the following heading: HIV or AIDS and atypical mycobacterial infections, *Mycobacterium avium* complex or *Mycobacterium avium intracellulare* and *M. kansasii*.

All information considered had to have been published in a peer review journal or presented at an international human immunodeficiency virus (HIV) meeting in abstract form. Inclusion/exclusion criteria essentially required that the information was relevant to the diagnosis, treatment or prevention of the specified opportunistic infection in HIV-positive individuals. Information of relevance to other related immunocompromised groups was also taken into consideration if the section authors felt relevant. Case reports were included and the review was not restricted only to clinical trials or meta-analyses. Search dates were from 1980 to January 2011.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Level of Evidence

Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well designed controlled study without randomization
IIb	Evidence obtained from at least one other type of well designed quasi-experimental study
III	Evidence obtained from well designed non-experimental descriptive studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Not stated

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Not stated

Description of Method of Guideline Validation

Not applicable

Evidence Supporting the Recommendations

References Supporting the Recommendations

DubÃ© MP, Torriani FJ, See D, Havlir DV, Kemper CA, Leedom JM, Tilles JG, McCutchan JA, Sattler FR. Successful short-term suppression of clarithromycin-resistant Mycobacterium avium complex bacteremia in AIDS. California Collaborative Treatment Group. Clin Infect Dis. 1999 Jan;28(1):136-8. PubMed

Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, Holland SM, Horsburgh R, Huitt G, Iademarco MF, Iseman M, Olivier K, Ruoss S, von Reyn CF, Wallace RJ Jr, Winthrop K, ATS Mycobacterial Diseases Subcommittee, American Thoracic Society, Infectious Disease Society of America. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007 Feb 15;175(4):367-416. [451 references] PubMed

Hardwick C, White D, Morris E, Monteiro EF, Breen RA, Lipman M. Montelukast in the treatment of HIV associated immune reconstitution disease. Sex Transm Infect. 2006 Dec;82(6):513-4. PubMed

Lipman MC, Carding SK. Successful drug treatment of immune reconstitution disease with the leukotriene receptor antagonist, montelukast: a clue to pathogenesis?. AIDS. 2007 Jan 30;21(3):383-4. PubMed

Pires A, Nelson M, Pozniak AL, Fisher M, Gazzard B, Gotch F, Imami N. Mycobacterial immune reconstitution inflammatory syndrome in HIV-1 infection after antiretroviral therapy is associated with deregulated specific T-cell responses: beneficial effect of IL-2 and GM-CSF immunotherapy. J Immune Based Ther Vaccines. 2005 Sep 25;3:7. PubMed

Zolopa A, Andersen J, Powderly W, Sanchez A, Sanne I, Suckow C, Hogg E, Komarow L. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. PLoS ONE. 2009;4(5):e5575. PubMed

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Accurate diagnosis and appropriate treatment of *Mycobacterium avium* complex and *Mycobacterium kansasii* infections in human immunodeficiency virus (HIV)-seropositive individuals

Potential Harms

- The dose of clarithromycin should not exceed 500 mg twice daily as higher doses have been associated with excess mortality.
- Rifabutin dosage should not exceed 300 mg/day (or 450 mg if given with efavirenz or 150 mg three times a week if given with ritonavir) as cases of uveitis have been reported with higher doses, especially when given with clarithromycin.
- *Mycobacterium avium* complex immune reconstitution inflammatory syndrome (MAC IRIS) can occur as focal disease presenting as regional lymphadenopathy, liver lesions, bone lesions or hypercalcaemia. This syndrome is usually self-limiting but can be severe and require adjunctive therapy.
- Significant drug–drug interactions also exist between rifabutin and antiretroviral agents (protease inhibitors and non-nucleoside reverse transcriptase inhibitors [NNRTIs]), which will affect the decision of whether to use rifabutin as a third agent and/or whether to modify the choice of the highly active antiretroviral therapy (HAART) regimen. Refer to Table 8.1 in the original guideline document for potential interactions between drugs used to treat atypical mycobacterial infections and antiretroviral drugs.
- Refer to Appendix 1 in the original guideline document for side effects of certain drug formulations.

Contraindications

Contraindications

- Refer to Table 8.1 in the original guideline document for potential interactions between drugs used to treat atypical mycobacterial infections and antiretroviral drugs.
- Refer to Appendix 1 in the original guideline document for contraindications of certain drug formulations.

Qualifying Statements

Qualifying Statements

- These guidelines are primarily intended to guide practice in the United Kingdom and related health systems. Although it is hoped they can

provide some guidance in developed countries there are some important distinctions in this environment and individual recommendations may not be as applicable in this setting.

- In the appendices in the original guideline document there is an A–Z of drugs used in the management of opportunistic infections. This is intended as a guideline but readers are advised to follow the discussion of dosing and the evidence for specific treatments provided in the text. In some cases alternative treatments are provided in the appendix in the original guideline document. These are not discussed in the text and these are mainly of historical interest and readers should be aware that these are not, in general, supported by the evidence base for treatments discussed in the text. It should also be noted that as evidence of drug toxicity, interactions, pregnancy risk and cost is rapidly evolving the table should be considered in association with the updated summary of product characteristics (SPC) for the agent and other relevant sources of drug information.
- Recommendations based upon expert opinion have the least evidence but perhaps provide an important reason for writing the guidelines: to produce a consensual opinion about current practice. It must, however, be appreciated that such opinion is not always correct and alternative practices may be equally valid. The recommendations contained in these guidelines should therefore be viewed as guidelines in the true spirit of the term. They are not designed to be restrictive nor should they challenge research into current practice. Similarly, although the British HIV Association (BHIVA) Opportunistic Infection Guidelines Group seeks to provide guidelines to optimize treatment, such care needs to be individualized and the authors have not constructed a document that they would wish to see used as a 'standard' for litigation.
- The clinical care of patients with known or suspected opportunistic infections (OIs) requires a multidisciplinary approach, drawing on the skills and experience of all healthcare professional groups. Moreover, these guidelines emphasize that inpatients with human immunodeficiency virus (HIV)-related disease often need rapid access to a variety of diagnostic tests and radiological interventions that may not be immediately available at local hospitals. Furthermore, expert interpretation of these tests by supporting specialties such as radiology, histopathology, microbiology and virology is often required. Optimal care of opportunistic infection can only be achieved by the close cooperation of these healthcare professionals and unless all are intimately involved in the care of patients, it is likely that the outcome will be less favourable. In keeping with BHIVA standards for HIV clinical care, patients needing inpatient care for HIV-related disease should ordinarily be admitted to an HIV centre or the relevant tertiary service in liaison with the HIV centre.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Mobile Device Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Fisher M, Ong E, Pozniak A. Mycobacterium avium complex and Mycobacterium kansasii. In: British HIV Association and British Infection Association guidelines for the treatment of opportunistic infection in HIV-seropositive individuals 2011. HIV Med. 2011 Sep;12(Suppl 2):75-82. [63 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Sep

Guideline Developer(s)

British HIV Association - Disease Specific Society

British Infection Association - Professional Association

Source(s) of Funding

British HIV Association

Guideline Committee

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Financial Disclosures/Conflicts of Interest

The British HIV Association (BHIVA) has a clear policy of declarations of interests within the Association:

- BHIVA requires that all members of guidelines writing groups, as well as any expert external peer reviewers, must declare all interests and membership of other committees retrospectively on an annual basis, to give protection to individuals working as members of writing groups.
- All members of guidelines writing groups must undertake a declaration of interests prior to serving on a writing group and this declaration is confirmed and repeated at the publication of each set of completed guidelines published.
- The details given in declaration forms are retained on a register at the Secretariat and can be made available for publication, if required.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the British HIV Association (BHIVA) Web site . Also available as a smartphone app from the BHIVA Web site .

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on July 30, 2014. This summary was updated by ECRI Institute on May 18, 2016 following the U.S. Food and Drug Administration advisory on Fluoroquinolone Antibacterial Drugs.

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