Mycobacterium Avium Complex

Synonyms: *Mycobacterium avium-intracellulare*, MAI

There are two discrete species in the *Mycobacterium avium* complex (MAC):

- *Mycobacterium avium* (M. avium).
- *Mycobacterium intracellulare* (M. intracellulare).

These two species are difficult to differentiate and therefore they are also referred to collectively as *Mycobacterium avium-intracellulare* (MAI). Although it might more logically be termed the *Mycobacterium avium-intracellulare* complex such nomenclature has not been adopted. They are both opportunistic pathogens that affect the immunocompromised, particularly HIV-positive individuals. They can also affect immunocompetent people, especially those with pre-existing lung disease. MAC is ubiquitous. However, only a minority of people exposed to MAC will acquire infection.

MAC can cause respiratory, gastrointestinal or disseminated infection in patients with AIDS. It usually only affects the lungs in the immunocompetent. It can cause lymphadenitis in children.[1] MAC infection is much less common in HIV-positive patients since the introduction of highly active antiretroviral therapy (HAART).

Epidemiology

- Before the advent of HAART, up to 30% of patients with HIV infection would develop disseminated MAC. This prevalence has now diminished significantly.
- A survey of French patients found that the infection was present in about 5% of HIV-infected patients who died.[2] These patients were more likely to be recently diagnosed and not taking HAART.
- Childhood lymphadenitis due to MAC is very rare but appears to be on the increase in developed countries.[3]

Pathophysiology

- *M. avium* causes 95% of AIDS-related MAC infections.[4]
- *M. intracellulare* causes 40% of MAC infections in the immunocompetent.
- Transmission is via the respiratory (inhalation) and the gastrointestinal (ingestion) routes. There are many environmental sources of MAC including:[5]
  - Piped hot water systems (household and hospital).
  - Aerosolised water (e.g., hot tubs).
  - House dust.
  - Soil.
  - Birds and farm animals.
  - Tobacco, cigarette filters and paper.
- The pathogens invade the respiratory or gastrointestinal mucosa and are carried to lymph nodes.
- They can then spread via the bloodstream to sites including the liver, spleen and bone marrow (this only tends to occur in the immunocompromised).
- Colonisation of the mucosa can occur without invasion and lymphatic spread. Spread can occur at a later stage as the CD4 count falls.
- In those with pre-existing lung disease, MAC usually just leads to pulmonary infection.
- The infection may (rarely) appear in elderly ladies with no pre-existing lung disease who chronically suppress the cough reflex and therefore allow respiratory secretions to stagnate. This is known as Lady Windermere syndrome.[6]
- MAC can also present as a hypersensitivity pneumonitis. This can occur in those exposed to water vapour containing MAC (commonly in poorly maintained indoor hot tubs or swimming pools).[7]

Risk factors

- HIV infection, particularly if not receiving prophylactic HAART.
- Other immunosuppression.
- Bronchiectasis.
- Cystic fibrosis.
- Chronic obstructive pulmonary disease (COPD).
- Pulmonary malignancy.
- Kyphoscoliosis or other skeletal abnormality reducing pulmonary ventilation.
- Mitral valve prolapse.

Presentation
Pulmonary MAC infection
Insidious onset. Features include:

- Cough.
- Excessive sputum production.
- Dyspnoea.
- Haemoptysis.
- Fever and night sweats.
- Fatigue.
- Weight loss.
- Nonspecific focal chest signs: crackles, wheeze, bronchial breathing, dullness to percussion.
- Clubbing (in cases with underlying bronchiectasis).

Disseminated MAC infection
CD4 count is usually <50 cells/mm$^3$. Features include:

- Fever (may present as pyrexia of unknown origin).
- Sweating.
- Malaise.
- Dyspnoea.
- Diarrhoea.
- Significant weight loss with marked wasting.
- Generalised lymphadenopathy
- Pallor.
- Tender hepatosplenomegaly.
- Cutaneous involvement.

Lymphadenitis

- Usually affects children aged 1-4. Cases in older people may be HIV-related.
- Most commonly presents with unilateral enlargement of cervicofacial lymph nodes.
- Affected lymph nodes include submaxillary, submandibular, parotid, preauricular, postauricular.
- Can resolve spontaneously.

Other presentations
These are rare. They can occur in immunocompromised or, occasionally, immunocompetent individuals.

- Bursitis.
- Septic arthritis.
- Osteomyelitis.
- Skin and soft tissue infections (commonly presenting as flesh-coloured/purple-red nodules, ulcers, folliculitis, abscesses or pustules).
- Tenosynovitis.
Differential diagnosis

- HIV-positive patients: other opportunistic infections such as Pneumocystis jirovecii pneumonia, toxoplasmosis, bacterial pneumonia, tuberculosis, cryptococcosis, cryptosporidiosis, histoplasmosis and leishmaniasis.
- Pulmonary disease in the immunocompetent: aspergillosis, infection with common bacterial pathogens, lung malignancy, haematological neoplasm causing immunosuppression, tuberculosis.
- Childhood lymphadenitis: actinomycosis, mumps, cat scratch disease and other causes of lymphadenopathy.

Investigations

Suspected disseminated infection

- HIV-positive patients need extensive investigation to assess the underlying status of their HIV infection and look for other causes of their symptoms. Consider HIV testing if HIV status is unknown.
- Blood cultures: mycobacterial culture media should be used. Acid-fast bacillus (AFB) staining.
- Culture of urine, stool, cutaneous lesions and sputum. AFB staining.
- CT scan of the chest: may show mediastinal lymphadenopathy and parenchymal involvement.
- CT/abdominal ultrasound scan: can show hepatosplenomegaly and retroperitoneal/periaortic lymphadenopathy.
- Biopsy of lymph nodes/bone marrow/cutaneous lesions: may be required to make the diagnosis/exclude other conditions. There are specific histological changes.
- Blood tests: to look for anaemia, pancytopenia, abnormal liver function, etc.

Pulmonary disease in the immunocompetent

- Sputum AFB staining: this is positive in most with MAC.
- Sputum culture: takes 1-2 weeks to detect the organism but doesn't differentiate between infection or just colonisation. A number of positive cultures are usually required for diagnosis and there are set criteria.
- CXR: may show cavitory changes, nodules and parenchymal involvement, particularly in middle and upper lobes, and mediastinal lymphadenopathy.
- CT scan of the chest: this may be needed to show lung involvement.
- Bronchoscopy and transbronchial biopsy/CT-guided needle biopsy: this may be needed to make the diagnosis. There are specific histological changes in the lung tissue.

Childhood lymphadenitis

- Needle aspiration or lymph node biopsy: followed by AFB staining and culture. Polymerase chain reaction (PCR) techniques can be used. There are also specific histological changes.
- Excision biopsy: this is often carried out.

Management

MAC is usually treated with two or three antibiotics for at least 12 months. Always seek microbiological advice before initiating treatment.

Disseminated infection

- Triple therapy with clarithromycin or erythromycin, ethambutol and rifabutin is usually most effective.
- There is a problem with rifabutin and drug interactions. It can also cause ocular toxicity (uveitis).
- Levofloxacin or amikacin are used in resistant cases.
- HAART should be commenced if the patient is not currently on antiretroviral treatment.
- In HIV-positive patients with a CD4 count <50 cells/mm$^3$, prophylaxis should be given as clarithromycin, azithromycin or, as second-line, rifabutin.
- Prophylaxis can probably be discontinued once the full benefits of HAART are apparent with CD4 count sustained above 100 and significant viral load reduction.
Pulmonary disease in the immunocompetent
- The usual regime is triple therapy with clarithromycin or erythromycin, ethambutol and rifabutin.
- Severe or unresponsive cases may require surgical excision of affected parts of the lung, but this is becoming less common.

Childhood lymphadenitis
- This should be treated by complete surgical excision, which is usually curative.[3]
- Antibiotics are not generally needed.

Complications
- Disseminated MAC can cause rapid deterioration and death in AIDS patients. Weight loss and anaemia are frequent complications. Cutaneous and brain abscesses can occur.
- Pulmonary MAC with extensive lung involvement can lead to worsening respiratory reserve and respiratory failure.

Prognosis
- Before the advent of newer macrolides and HAART, the outlook for someone with AIDS and disseminated MAC was very poor with a life expectancy of four months.
- With active treatment with antibiotics and HAART, the outlook has now improved considerably.[4]
- MAC lymphadenitis may undergo spontaneous regression in children. If untreated, rupture and sinus formation can occur.
- Pulmonary MAC infection is usually responsive to treatment, depending on the severity of the underlying disease.
- Focal nodular disease has the best prognosis and tends to be fairly benign. Recovery rates are still high (90%) in those with more extensive disease, but relapse can affect up to a fifth.[5]

Prevention
Prophylaxis for MAC is essential in susceptible HIV-positive individuals with CD4 counts <50 cells/mm³.[4]

Further reading & references

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