Opportunistic Infections: Disseminated Mycobacterium Avium Complex (dMAC)

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Learning Objectives:

1. Recognize the most common clinical manifestations of disseminated mycobacterium avium infection (MAC) and understand how to make the diagnosis.
2. Learn the current treatment guidelines for disseminated MAC and how to monitor the response to therapy.
3. Understand the current guidelines for primary and secondary prophylaxis against disseminated MAC in patients with HIV/AIDS.

Case 1: Mr. C is a 48 year old man with history of HIV/AIDs who presents to clinic to re-establish care. He reports that he has not been on ARVs for the past 2 years due to insurance issues and has not been seen by a medical provider since then. He complains of a 40-pound weight loss over the past year, as well as several weeks of intermittent fevers, night sweats, poor appetite, and fatigue. He denies any rash, cough, vomiting, or diarrhea. He has not been taking any medications. Physical exam reveals a thin man who appears older than his stated age. His exam is otherwise unremarkable. Labs are notable for a CD4 count of 2 cells/mm^3 and an HIV viral load of 360,000 copies/ml. He is also noted to have a new mild anemia. He is admitted to the hospital where extensive infectious work-up reveals blood cultures growing mycobacterium avium complex (MAC).

Questions:

1. How is disseminated MAC acquired and what are the risk factors for disease?

Disseminated mycobacterium avium complex (dMAC) includes several species of non-tuberculosis mycobacterium including *Mycobacerium avium*, *Mycobacterium kansasii*, *Mycobacterium intracellulare,* as well as several other species. dMAC is thought to be acquired from the environment, particularly through water source, via inhalation through the respiratory tract or ingestion through the gastrointestinal tract. There has not been any convincing data to suggest that it is transmitted from human-to-human contact.

In immunocompetent hosts, dMAC organisms are effectively ingested and killed by tissue macrophages. In patients with advanced HIV with severe immunocompromised, macrophage-mediated killing is defective, allowing uncontrolled, intracellular replication of dMAC. These infected macrophages then rupture, releasing organisms throughout the lymphatics and bloodstream. As a result, patients who are infected with dMAC usually present with disseminated, multi-organ disease.

Risk factors for dMAC include a CD4 count less than 50 cells/mm^3, HIV RNA plasma levels greater than 100,000 copies/ml, ingestion of hard cheese, and respiratory or GI colonization of MAC.

2. What are the most common clinical manifestations of disseminated MAC disease?

In HIV infected patients, MAC tends to present as disseminated disease affecting multiple organ systems. Clinical signs and symptoms include fever, night sweats, weight loss, fatigue, malaise, anorexia, diarrhea, abdominal pain, and cough. Exam may be notable for hepatomegaly, splenomegaly, and adenopathy (though less often peripheral and more often para-tracheal, para-aortic, or retroperitoneal). Labs may be notable for elevated liver transaminases and alkaline phosphatase, elevated LDH, as well as bone involvement (anemia and neutropenia).

3. How is the diagnosis of dMAC made?

Diagnosis of disseminated MAC requires the isolation of the organism from a sterile site. A single blood culture has a high diagnostic yield (90–95% sensitive). Cultures usually grow out within two weeks and are finalized by eight weeks. Once sufficient growth is achieved, the diagnosis of MAC can be made in few hours with the use of DNA probes. The diagnosis can also be made by identification of MAC from other sterile sites such as bone marrow, liver or lymph node biopsy.

4. What are the current recommendations for treatment of dMAC?

Initial treatment for dMAC should consist of two or more anti-mycobacterial agents in order to avoid the development of resistance:

- **Clarithromycin** is the preferred first agent, as it has been studied more extensively than azithromycin and is associated with rapid MAC clearance from the blood. Azithromycin may be used instead if there is concern for drug interactions or intolerance with clarithromycin.[1] Susceptibility testing to clarithromycin and azithromycin from MAC isolates is recommended.
- **Ethambutol** is the second recommended agent to treat dMAC.
- **Rifabutin** may also be added as a third agent, as some studies suggest this may improve survival and reduce risk of drug resistance; however, these studies were done before effective ART was available.
    - Furthermore, the addition of a third or fourth drug to the regimen may be considered in patients with high mycobacterial loads (more than 2 log10 colony forming units per mL of blood), in the absence of effective ARTs, in patients with advanced immunosuppression, or in the setting of concern for drug resistance.
    - Third or fourth regimen drugs include fluoroquinolones (levofloxacin, moxifloxacin), amikacin, or streptomycin (both which are injectable agents).

Side effects associated with clarithromycin and azithromycin include nausea, vomiting, abdominal pain, abnormal taste, elevated LFTs, and hypersensitivity reactions. Rifabutin may be associated with uveitis, arthralgias, and neutropenia. It also decreases the effectiveness of oral contraceptives.

[1] One important drug actions to note are that clarithromycin is a CYP450 inhibitor isoenzyme 3A4. In patients who are on atazanavir, the dose of clarithromycin should be reduced by 50%. It should also be avoided in any patients on etravirine, in which case azithromycin should be used instead.

Ethambutol can cause optic neuritis and blindness, especially in patients with co-existing renal dysfunction, and patients should be followed closely by ophthalmology.

Case continued: The patient is started on clarithromycin 500 mg PO BID and ethambutol 15 mg/kg PO daily for disseminated MAC. He is also started on trimethoprim-sulfamethoxazole for PCP prophylaxis. The patient is discharged and returns to you two weeks later for follow up. He states that he is no longer having fevers or night sweats but does complain of persistent fatigue and poor appetite. He asks you how long he will need to remain on treatment for.

5. What type of monitoring for response to therapy should be done?

Improvement in clinical symptoms should improve within 2-4 weeks after therapy, but in patients with more extensive disease or immunosuppression, clinical response may be more delayed. Only patients who fail to have a clinical response to their initial treatment 4-8 weeks after initiation should have repeat blood cultures for MAC obtained. Treatment failure is defined by the absence of a clinical response and persistent mycobacteremia after 4-8 weeks of treatment. Susceptibility testing should then be done on MAC isolates and a new multi-drug regimen should be started, including at least two new drugs not used previously to which the isolate is susceptible.

6. What is the recommended duration of therapy?

The patient should complete at least a 12 month course of treatment for dMAC, remain asymptomatic without symptoms of dMAC, and have an increase in their CD4 count >100 cells/mm^3 for at least 6 months. Some patients may require lifelong therapy. Resume secondary prophylaxis if the CD4 count decreases to less than 100 cells/mm^3.

7. When should anti-retroviral treatment (ART) be initiated in this patient?

ART should be started 2 weeks after initiation of anti-mycobacterial therapy. This is to reduce complications associated with immune reconstitution inflammatory syndrome (IRIS), as well as to reduce the risk of drug interactions. Start ART as soon as possible after 2 weeks, however, to reduce the risk of developing other OIs and to improve the patient's immunosuppression. If the patient was previously on ART, it should be continued.

Case 2: Mr. F is a 60 year old man with recently diagnosed HIV/AIDS with a CD4 count of 17 cells/ mm^3. After a thorough work-up he is ruled out for active opportunistic infections. He is started on ART after extensive counseling, as well as Bactrim for prophylaxis against toxoplasmosis and PCP. Given his low CD4 count, you are also concerned about dMAC prophylaxis.

8. What are the indications for primary prophylaxis against disseminated MAC? What are the preferred drugs for primary prophylaxis?

HIV infected adults should receive prophylaxis against disseminated MAC disease if they have CD4 counts less than 50 cells/mm^3. Disseminated MAC should be ruled out by clinical assessment before initiating prophylaxis.

Azithromycin or clarithromycin are the preferred drugs for prophylaxis. While azithromycin plus rifabutin is more effective than azithromycin alone for preventing dMAC, due to the potential for adverse effects, potential for drug interactions, and cost, this regimen is not recommended. Rifabutin alone may be an alternative, however, for patients who cannot tolerate macrolides.

9. When can primary prophylaxis against dMAC be discontinued?

Treatment for primary prophylaxis against dMAC should be discontinued when the patient has an increase in his/her CD4 count greater than 100 cells/mm^3 for three months or more. This is based on data from two randomized placebo controlled studies, as well as observational data, which has suggested that such patients have minimal risk of acquiring dMAC disease if discontinued. Primary prophylaxis for dMAC should be restarted if CD count decreases to <50 cell/mm^3.

Recommended Reading

"*Disseminated Mycobacterium avium complex Disease*". Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. AIDS Info. Last updated 5/7/13. https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/326/mac

Additional References

1. 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*. Nov 1 2003;37(9):1234-1243. Available at http://www.ncbi.nlm.nih.gov/pubmed/14557969

2. Mandell, Douglas and Bennett's Principles and Practices of Infectious Diseases, 8th edition. Churchill Livingstone; 2015. 253, 2832-2843. Available online https://www.clinicalkey.com/#!/content/book/3-s2.0-B9781455748013002538