

Case SIGNOUT

79 year-old woman admitted for shortness of breath and pulmonary edema with a history of MAC pulmonary disease and diastolic dysfunction. She received therapy for MAC lung disease several years ago but it was aborted secondary after an adverse drug reaction to a clarithromycin-based regimen. The patient still has residual bronchiectasis on lung CT.

Clinical question: What treatment options exist for MAC infection in a non-HIV infected host and what are their efficacy? Are there treatment options that do not include clarithromycin?

Ovid MEDLINE(R) 1966 to January Week 3 2005

Search History Results Display

1 mycobacterium avium.mp. or Mycobacterium avium/	5487
2 mycobacterium intracellulare.mp.	431
3 mycobacterium avium complex.mp. or Mycobacterium avium Complex/	2344
4 mycobacterium avium intracellulare.mp./	2468
5 1 or 2 or 3 or 4	5623
6 DRUG THERAPY, COMBINATION/ or therapy.mp. or DRUG THERAPY/	861391
7 macrolide.mp. or MACROLIDES/	7276
8 azithromycin.mp. or AZITHROMYCIN/	2564
9 clarithromycin.mp. or CLARITHROMYCIN/	4358
10 7 or 8 or 9	12234
11 5 and 6 and 10	263

Caveats...

There are no randomized controlled trials that compare different macrolide containing regimens such as clarithromycin versus azithromycin for MAC pulmonary disease in non-HIV infected hosts.

There are no randomized controlled trials that compare non macrolide based regimens with macrolide based regimens.

Azithromycin-containing regimen for the treatment of Mycobacterium avium complex lung disease. Giffith DE, et al. CID. 2001 (32): 1547-53, 2001 June.

Group	Criteria or definition	n
Population	Must have > 2 sputum cx (+) and chest radiography consistent with MAC disease.	
Exclusion criteria	Exclusion criteria: pregnancy, life-threatening illness with no prior therapy for MAC lung disease, resistance to macrolides in a pretreatment MAC isolate , and identified risk factors or known HIV. Patients were considered for inclusion into the study, regardless of previous therapy for MAC.	
Treatment groups:	<p>Three arms: (all pts. rec'd streptomycin TIW until culture showed azithromycin sensitivity)</p> <p>A. Azithromycin daily 300–600 mg Ethambutol daily, 25/mg/kg/d for 2 months then 15mg/kg/d Rifabutin daily, 150-300 mg</p> <p>B. Azithromycin TIW Ethambutol daily, 25/mg/kg/d for 2 months then 15mg/kg/g Rifabutin daily , 150-300 mg</p> <p>C. Azithromycin TIW Ethambutol TIW, 25/mg/kg/TIW Rifabutin TIW, 300-600 mg</p>	<p>103</p> <p>32</p> <p>22</p> <p>49</p>
No treatment group	No placebo group	
Methods	One sputum was taken each week during therapy and culture negativity was defined as success.	

Primary endpoint: 1) Treatment success = negative cultures for 12 months while on therapy.
2) Treatment failure = sputum culture positivity after at least 6 months on therapy.

Are the results valid?

Randomized?	No.
All patients accounted for at end?	No (92/103 followed-up)
Intention to treat?	No (Outcomes for 92/103)
Blinding?	No
Equal treatment of groups?	No
Did randomization work?	n/a

Endpoint	Result – Culture Cure (%)	Signific.	ARR	NNT
Regimen A	59	NS		
Regimen B	55	NS		
Regimen C	65	NS		
Morbidity	Result – Adverse effect of azithromycin (%)	Signific.	ARI	NNT
Regimen A	21	P=0.05		
Regimen B	10			
Regimen C	5			

There was a significant difference in response rates when comparing patients who did not respond to therapy on a previous 6-month or longer course with those who did not respond. Of the patients who had received previous therapy, only 9 (38%) of 24 were successfully treated in this trial, compared with success with 46 (68%) of 68 of those patients with no previous therapy (P<0.01).

Can I apply these results to my patient? Clearly this is a flawed trial in many ways including the failure to do a true ITT analysis, failure to randomize (or explain it if it was done), and failure to look at adherence.

Comparison of my patient to trial patient – If patient makes two cx (+) sputums she qualifies as long as she is not resistant to macrolides. She would be expected to do worse considering she is a retreatment patient.

Limitation:

- Because of the limited number of good treatment options in this disease, good comparison trials have not been done.
- I do not think I missed any important studies because in addition to the search I looked at several reviews of the topic and they mentioned the lack of data as well.

Despite its flaws, this trial is somewhat reassuring to me in that a clinical experience with azithromycin exists and the drug appears to be well tolerated and somewhat effective over the long-term.

Background

Mycobacterium avium and mycobacterium intracellulare are grouped together as mycobacterium avium complex (MAC) or mycobacterium avium intracellulare (MAI) because they have similar clinical presentation, radiographic appearance and response to therapy. **In HIV infected patients they cause disseminated disease and but, in patients without immunocompromised states, they can cause chronic pulmonary infection.**

Most patients in older reports were older, were male and had chronic lung disease. In more recent reports most patients, especially with fibronodular disease were elderly females without prior lung disease. Patients who are thin, have kyphoscoliosis or pectus excavatum appear at increased risk.

Two clinical categories: **(1) fibronodular disease with bronchiectasis: almost exclusively elderly thin women with no prior history of lung disease most often in the middle lobe and/or lingula** (2) fibrocavitary changes: older patients with a history of chronic lung disease most often in upper lungs.

Symptoms include chronic cough, sputum and constitutional symptoms if patients have extensive lung disease. Early disease is often discovered incidentally on CXR.

Diagnosis

The 1997 ATS statement recommended that **a minimum of three sputum specimens or other respiratory specimens be stained and cultured** in symptomatic patients presenting with possible pulmonary MAC. **The rationale for the requirement for multiple positive culture results is that MAC is present in tap water,** even in hospitals, and false-positive culture results may occur.

Treatment

“Results with antituberculosis medications improved after the introduction of ethambutol and rifampin in the mid 1960s and early 1970s. The reported rates of treatment success have ranged from 20 to 90% in individual studies. Much of this variability depended on whether an intention-to-treat strategy was used and whether relapses were included in the calculation of treatment success. When all patients were included the cure rate was approximately 40%.”

The development of the newer macrolides clarithromycin and azithromycin was important in the therapy of MAC, particularly because the drugs accumulated in macrophages and appeared to be effective against this intracellular organism. They showed efficacy in disseminated disease in HIV infected patients but resistance developed when used alone in MAC pulmonary disease. The use of ethambutol and a rifamycin appear to prevent the emergence of macrolide resistance. Clarithromycin, while effective, is more likely to result in adverse effects (GI upset, taste perversions and allergic reaction) and in initial studies about 20% discontinued therapy.