

nonmacrolide-containing regimens [137]. Macrolide susceptibility has been a consistent predictor of treatment success for MAC pulmonary disease, whereas susceptibility to most other drugs has not been a predictor [112]. In a postmarketing study from Japan, among 271 patients with macrolide-susceptible MAC pulmonary disease who received a clarithromycin-based regimen, sputum culture conversion to negative occurred in 95% [136]. Although no well-designed randomized trials of macrolide therapy have been performed, the panel felt that macrolides are a critical component of MAC treatment based on poor patient outcomes if macrolides are not included in the treatment regimen. As such the panel members voted unanimously to make a strong recommendation despite the very low certainty of estimates of effect.

Question IV. In patients with newly diagnosed macrolide-susceptible MAC pulmonary disease, should an azithromycin-based regimen or a clarithromycin-based regimen be used?

Background: The macrolides are considered to be key components in treatment regimens against MAC pulmonary disease. The 2007 Guideline expressed a preference for azithromycin over clarithromycin in initial treatment regimens [4].

Recommendation

1. In patients with macrolide-susceptible MAC pulmonary disease we suggest azithromycin-based treatment regimens rather than clarithromycin-based regimens (conditional recommendation, very low certainty in estimates of effect).

Summary of the Evidence: Both clarithromycin and azithromycin have demonstrated activity in MAC pulmonary disease, with early studies demonstrating some efficacy for monotherapy [117, 138], and subsequent studies demonstrating efficacy as part of multi-drug regimens administered both daily [83] and 3 times weekly [22, 139, 140]. Limited data are available from comparisons of treatment outcomes in patients treated with clarithromycin versus azithromycin [22, 141], and no significant difference was found in either microbiologic efficacy or tolerability, although there was a nonsignificant trend toward lower tolerability for clarithromycin in 1 study [141]. The relative and absolute effect estimates and 95% CIs for each outcome (Table E3.4) and discussion of value preferences, feasibility, cost, acceptability, and health inequality (Table E4.4) can be found in the supplement.

A recent systematic review reported no clinically significant differences between azithromycin and clarithromycin in sputum culture conversion at 6 months, end of therapy, or on sustained conversion after treatment nor was there a difference in the acquisition of macrolide resistance [133]. However, azithromycin has less potential for drug-drug interactions than

clarithromycin [142]. The drug-drug interactions are particularly relevant when a rifamycin (rifampicin or rifabutin) is given concurrently; azithromycin serum concentrations are affected less by concurrent rifampicin or rifabutin administration than clarithromycin, but the interaction is bidirectional for clarithromycin and rifabutin, leading to increased concentration of rifabutin (but not rifampicin), which has been associated with uveitis [111, 143–145]. Other considerations that would favor azithromycin over clarithromycin include a lower pill burden, once daily dosing, and possibly lower costs.

Justification and Implementation Considerations: The preference for azithromycin is primarily based on the expert panel's perception of better tolerability of azithromycin and fewer drug-drug interactions mediated by the cytochrome P450 system [146] than with clarithromycin. Both azithromycin and clarithromycin have been reported to be associated with severe adverse effects, including sudden death presumably mediated by QTc prolongation [147, 148]. However, a systematic review that evaluated adverse events in people taking macrolides versus placebo for any indication reported no increase in cardiac disorders or mortality when compared with placebo [149]. Electrocardiographic monitoring may be considered for patients when concurrent medications that prolong the QTc interval are being used. In the same systematic review noted above [149], hearing loss was reported more frequently in patients taking macrolides than placebo; however, the differences were not statistically significant, and there were no studies of clarithromycin to address differences between macrolides. In older patients, hearing loss and gastrointestinal symptoms have been associated with higher doses (600 mg daily) and serum concentrations of azithromycin [150], whereas bitter taste, nausea, and elevated hepatic enzymes have been associated with higher doses (1000 mg twice daily) of clarithromycin [151]. Of note, all studies included some patients who did not tolerate azithromycin and were successfully switched to clarithromycin and *vice-versa*. Switching from one agent to the other is a strategy that may be considered in case of intolerance. The panel felt that azithromycin was preferred over clarithromycin because of likely better tolerance, less drug interactions, lower pill burden, single daily dosing, and equal efficacy. In places where azithromycin is not available, clarithromycin is an acceptable alternative although more drug interactions are possible.

Question V. Should patients with MAC pulmonary disease be treated with a parenteral amikacin or streptomycin-containing regimen or without a parenteral amikacin or streptomycin-containing regimen?

Background: MAC isolates are usually susceptible in vitro to amikacin. Streptomycin was used in early noncomparative treatment trials during the initial months of treatment for both cavitary and nodular/bronchiectatic MAC pulmonary disease [83, 138]. Parenteral aminoglycoside therapy was recommended in some previous NTM guidelines during the initial