In the Literature

**Clinical Therapeutic Implications of Macrolide Resistance in Mycoplasma pneumoniae**


The emergence of macrolide resistance in *M. pneumoniae* was recently addressed in this section of the journal (see “Macrolide-Resistant Mycoplasma pneumoniae” in the 1 April 2010 issue). This problem was originally observed in Japan, followed by identification of macrolide resistance in China and Europe. Most recently, 2 children with community-acquired pneumonia in Alabama who had poor responses to azithromycin therapy were found to be infected with *M. pneumoniae* isolates carrying A2063G mutations in their 23S rRNA genes, an alteration associated with macrolide resistance [1]. Although these 2 children were identified because of poor responses to macrolide (azalide) therapy, the overall clinical implications of this resistance as a vir macrolide therapy has been poorly defined. This is especially important in children because of the absence of known effective alternative therapies, given the potential problems associated with the use of tetracycline and fluoroquinolones in this age group. Although in vitro macrolide resistance in *M. pneumoniae* appears to be a growing problem, its clinical relevance has not been adequately defined. This issue has now been directly addressed in a cohort study by Matsubara and colleagues in Tokyo, Gunma, and Yokohama, Japan.

Of 94 strains of *M. pneumoniae* isolated from 94 children, 30 (31.9%) were resistant to macrolides, as determined by both in vitro susceptibility testing and full-length sequencing of the 23S rRNA gene. The 90% minimum inhibitory concentration (MIC90) for drug-resistant strains for erythromycin, clarithromycin, and erythromycin was ≥64 µg/mL, whereas the MIC90 for drug-susceptible strains ranged from 0.000975 µg/mL to 0.0156 µg/mL for these 14- and 15-membered ring macrolides. The MIC90 of the 16-membered ring macrolides, rokitamycin and josamycin, were 16 µg/mL and 64 µg/mL, respectively. The MIC90 for macrolide-susceptible strains and for macrolide-resistant strains to levofloxacin and minocycline were each 1.0 µg/mL.

A total of 25 patients (17 infected with macrolide-susceptible strains and 8 infected with macrolide-resistant strains) were excluded from the analysis of response to therapy, leaving 47 and 22 patients infected with macrolide-susceptible and macrolide-resistant strains, respectively, for study. The mean duration of fever after initiation of macrolide therapy was 1.5 days among patients infected with macrolide-susceptible strains and 4.0 days among those infected with macrolide-resistant strains (P<.001), whereas cough persisted for a mean duration of 7.0 and 11.4 days, respectively (P<.001). The clinical efficacy of treatment with a macrolide was 91.5% when the isolate was susceptible to macrolides and only 22.7% when it was resistant (P<.01).

Although a number of relevant elements are missing from this publication, such as details regarding treatment, it provides reasonable evidence that macrolide resistance is clinically relevant. Reports of macrolide resistance in *M. pneumoniae* in the United States remain rare, but this may be associated with a lack of testing. At any rate, increasing resistance is inevitable, and therapeutic options must be considered. Although fluoroquinolones and tetracyclines are effective alternatives for therapy in adults, the potential toxicity of these agents in children leaves no demonstrably effective alternative choices. Possibilities, however, may include ketolides and, for intravenous therapy, quinupristin-dalfopristin. In the mean time, it is important that surveillance be maintained for the detection of macrolide resistance in *M. pneumoniae*.

**Reference**


**Pseudoleukocytosis**


Geara and colleagues describe a 5-year-old man with known chronic hepatitis C virus (HCV) infection and a petechial skin eruption of 2 months’ duration. The patient was admitted to the hospital with acute pulmonary edema and acute renal failure due to membranoproliferative glomerulonephritis secondary to mixed cryoglobulinemia. Although the patient’s white blood cell count was initially reported to be <12,000 cells/mm³, after transfer from the intensive care unit, it reportedly fluctuated between 24,000 and 96,000 cells/mm³. Examination of his peripheral blood smear, however, failed to confirm the presence of leukocytosis. Furthermore, after the patient underwent plasmapheresis, the laboratory reported that his white blood cell count was normal.

All white blood cell counts had been performed using an automated system. In electronic cell counters, individual cells are subjected to an electric current as they flow through an aperture, and the increased resistance associated with each cell is detected. Cryoglobulins may precipitate at low temperatures, producing particles mistaken for cells by the counter. The likelihood of this occurrence depends on the concentration of cryoglobulin, its thermal
amplitude, and the conditions to which the sample is exposed.

Pseudoleukocytosis due to cryoglobulinemia has previously been reported, as have pseudothrombocytosis and pseudolymphocytosis. In vitro clumping of platelets may also cause pseudoleukocytosis. Although these are apparently rarely encountered phenomena, clinicians should be aware of these occurrences.

**Treatment of Pneumocystis jirovecii Pneumonia (PCP) When Trimethoprim-Sulfamethoxazole (TMP-SMZ) Fails or Cannot Be Used**


Current guidelines indicate that TMP-SMZ is the preferred choice for the treatment of PCP [1]; they go on to list dapsone plus trimethoprim, primaquine plus clindamycin, and atovaquone suspension as alternatives for the treatment of mild-to-moderate disease, but fail to indicate a preference of one over the others. For moderate-to-severe disease, the guidelines list clindamycin-primaquine and intravenously administered pentamidine as alternatives but, in this case, state that the latter is generally the drug of second choice for severe disease.

Helweg-Larsen and colleagues retrospectively reviewed 1122 patients with 1188 episodes of PCP from 3 observational cohorts observed during 1989–2004 in Milan, Italy; Copenhagen, Denmark; and London, United Kingdom. TMP-SMZ was used as first-line therapy in 81% of episodes, whereas intravenous pentamidine was used in 7% and clindamycin plus primaquine were used in 6%. The initial therapy was altered in 311 episodes (26%); this occurred because of toxicity in 207 episodes and treatment failure in 104 episodes, whereas 22 episodes were excluded from analysis because changes in the treatment regimen occurred before the patients had received 4 days of therapy. The median time to change in first-line therapy was 10 days.

First-line therapy with TMP-SMZ was continued without change in 79% of episodes, clindamycin-primaquine was continued without change in 81%, and intravenous pentamidine was continued without change in 60% (*P* < .001). The 3-month survival rates for patients receiving these initial therapies were 85%, 81%, and 76% (*P* = .09), respectively. Adjustment for confounders using multivariable analysis found that first-line treatment with intravenous pentamidine was associated with a significantly increased risk of death by 3 months (hazard ratio, 2.0; 95% confidence interval, 1.2–3.4). The choice of second-line therapy was TMP-SMZ in 9% of episodes, pentamidine in 70%, and clindamycin-primaquine in 18%; 3-month survival rates were 85%, 60% (*P* = .01), and 87%, respectively. Multivariable analysis identified an increased risk of death associated with pentamidine therapy versus TMP-SMZ therapy (hazard ratio, 3.3; 95% confidence interval, 2.2–5.0).

The investigators conclude that TMP-SMZ should remain first-line therapy and that, for second-line therapy, clindamycin-primaquine is preferred over intravenous pentamidine. The roles of other regimens (eg, atovaquone, dapsone plus trimethoprim) could not be assessed because of the small number of cases. Because all of the alternatives have at least 1 component that is available only in the United States for oral administration (trimetrexate is no longer commercially available), intravenous pentamidine may have to be used for some patients requiring parenteral therapy.

Evidence is accumulating of the relative inefficacy and toxicity of pentamidine. A small, randomized trial demonstrated better tolerability and improved survival with TMP-SMZ treatment versus intravenous pentamidine [2]. Other trials involving patients with mild-to-moderate disease have compared TMP-SMZ with clindamycin plus primaquine [3] and, in a 3-arm study, TMP-SMZ with clindamycin plus primaquine and with dapsone plus trimethoprim [4]; results were comparable for all regimens studied. A small retrospective study also has found better outcomes with clindamycin-primaquine than with intravenous pentamidine as second-line therapy [5]. It appears that pentamidine should be used as an alternative to TMP-SMZ only when treatment must be parenterally administered.

**References**


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