In the Literature

**Artemisinins in Danger**


Artemisinin derivatives, including artesunate and artemether, are the most effective available agents for the treatment of malaria due to *Plasmodium falciparum*. Preservation of their usefulness, by avoidance of the emergence of malarial resistance, is of critical importance.

Vijaykadga and colleagues examined the response to treatment of infections due to *P. falciparum* in 9 provinces in Thailand with international borders. All patients received a single dose of primaquine on day 0; administration of all therapy was observed. The rates of response to mefloquine monotherapy, which was used in 4 provinces, were low (62%, 75%, 89.7%, and 94%). In contrast, the response rates to combination therapy with mefloquine and artesunate in a 2-day regimen (the World Health Organization recommends a 3-day regimen) ranged from 93.8% to 97.7% in 4 provinces, but the rate was only 78.6% in Trat, which borders Cambodia and where this combination of antimalarials has been used since 1995. Genotyping to confirm recrudescence, rather than reinfection, was not performed, nor was in vitro testing or mutational analysis for evidence of resistance.

Jambou and colleagues performed in vitro susceptibility testing by measurement of H’-hyoxanthine incorporation by 530 *P. falciparum* isolates obtained in Cambodia and Senegal in 2001 and in French Guiana in 2002–2003. The introduction of artemether into Cambodia had been carefully controlled, with the drug used only in combination with mefloquine. In contrast, in Senegal, artemisinin derivatives have been available in the private sector, and in French Guiana, illegally imported formulations have been available and used for self-medication.

The highest IC<sub>50</sub>s of artemether detected in French Guiana and Senegal (117 nmol/L and 45 nmol/L, respectively) were greater than the maximum values previously reported from any country. Examination of the sequences of 2 genes encoding potential artemisinin targets (*Pfctp* and SERCA-*PfATP6*) in 60 isolates identified 23 polymorphisms in the latter but none in the former. All mutations detected in isolates recovered from Cambodia were synonymous. One isolate from Senegal had 2 mutations in SERCA-*PfATP6* that were associated with a very high artemether IC<sub>50</sub>. SERCA-*PfATP6* mutations were identified in 7 isolates from French Guiana; 6 of these 7 consisted of S769N mutations. This substitution was very strongly associated with elevated artemether IC<sub>50</sub>s.

The current introduction of artemisinins into sub-Saharan Africa, where malaria transmission occurs at a very high rate, increases the threat of the development of resistance to this agent. This risk is especially high with its use as monotherapy. The World Health Organization has recognized this risk and has called for restriction of the availability of this class of drugs to inclusion in combination therapies [1]. It is important, however, that the agent used in combination with artemisinins also be highly active against *P. falciparum* in the region of use. If the protozoan is resistant to the second agent, combination therapy becomes monotherapy, with all the attendant risks of artemisinin resistance. Unfortunately, artemether resistance appears to have already reared its ugly head in French Guiana and Senegal and possibly in the Thai province of Trat.

**Reference**


**An Unexpected and Lethal Cause of Community-Acquired Pneumonia (CAP): Acinetobacter baumanii**


Leung and colleagues in Hong Kong retrospectively evaluated the clinical features of 19 patients with CAP due to *A. baumanii*. None of the patients had received either antibiotics or systemic corticosteroids in the previous 2 months, and none had been hospitalized in the previous year. The mean age of the patients with CAP due to *A. baumanii* was 76.2 years, and 84% of them were male; all but 1 had underlying chronic illness, 84% had smoked tobacco at some time, and almost two-thirds had chronic obstructive pulmonary disease (COPD). Most had an abrupt onset of illness and presented with severe respiratory distress. The mean WBC count was only 10,600 cells/mm<sup>3</sup>. Six (32%) of the 19 patients were bacteremic. The mean APACHE II score at presentation was 14.1, and 84% developed acute respiratory distress syndrome, whereas 58% required pharmacologic blood pressure support. Two-thirds of the patients received inadequate empirical antibiotic therapy. Fifty-eight percent of all patients died.

A comparison with 74 patients with hospital-acquired pneumonia due to *A. baumanii* found that patients with CAP due to this organism were more likely to have been smokers at some time, to have COPD, to be bacteremic, to develop acute respiratory distress syndrome and/or dis-
seminated intravascular coagulation, and to die—and to do so much more quickly (mean time to death, 8 vs. 103 days).

Although only 16% of the patients with CAP in this report were known to be alcoholics, excess alcohol consumption has been suggested to be a risk factor in other studies, and a study from Darwin, Australia, found that 10% of evaluated alcoholics had pharyngeal colonization with A. baumanii [1]. Otherwise, previous studies have provided largely concordant descriptions of CAP due to this organism. Typically, the patient is elderly, has comorbidities (commonly COPD), and presents with an acute onset of febrile illness and respiratory distress. Leukocytosis may be absent, and disseminated intravascular coagulation and hypotension are common, as is the need for mechanical ventilation. The mortality rate is high.

For the patients described by Leung and colleagues who were admitted to the medical ward, the application of the current Infectious Diseases Society of America guidelines for CAP (in which Acinetobacter species are not mentioned) would lead to provision of initial empirical antibiotic therapy with “a respiratory fluoroquinolone alone or an advanced macrolide plus a β-lactam” (cefotaxime, ceftriaxone, ampicillin-sulbactam, or ertapenem) [2]. For patients who were admitted directly to an intensive care unit and who were not be-
twenty the evolving resistant patterns of A. baumanii [1]. Otherwise, previous studies have provided largely concordant descriptions of CAP due to this organism.

The clinical success rate in the microbiologically evaluable population was 91.4% among those receiving the 750-mg dose for 5 days and 88.6% among those assigned the 500-mg dose for 10 days. The response rates for patients infected with Haemophilus influenzae, Streptococcus pneumoniae, or Moraxella catarrhalis all exceeded 90% in each treatment arm. Staphylococcus aureus was recovered from 37 patients, representing 12.3% of the microbiologically evaluable population; responses were achieved in 10 (83.3%) of 12 patients who received the 500-mg dose and in 19 (76.0%) of 25 who received the 750-mg regimen. The incidence of adverse events did not differ in the 2 treatment groups.

This study demonstrates comparable efficacy of the 2 regimens. The short-course, higher-dose regimen has a number of potential beneficial features, including a likelihood of improved compliance, more-favorable pharmacodynamics, reduced risk of selection of gyrase or topoisomerase mutations, and, as seen in a comparable study of CAP [1], more rapid symptom resolution. Unfortunately, none of these features were evaluated by the investigators.

One finding of note was the 12.3% incidence of infection with S. aureus among patients with acute paranasal sinusitis. This finding was not simply the result of contamination of endoscopic specimens for patients with nasopharyngeal colonization, because it occurred just as frequently among patients whose specimens were obtained by maxillary sinus puncture. This result should raise an alarm, given the explosion of community-acquired infection with methillin-resistant S. aureus. The investigators, unfortunately, did not report the results of antibiotic susceptibility testing.

Reference