Prescribe Fluoroquinolones With Care in CAP

BY DIANA MAHONEY
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MONTREAL — Respiratory fluoroquinolones for the treatment of community-acquired pneumonia should generally be restricted to hospitalized patients to minimize the development of resistance to the drugs among respiratory pathogens as well as colonization by other pathogens, said Thomas M. File Jr., M.D.

"Outpatient studies have shown that many [community-acquired pneumonia] patients who are given quinolones could have been given other agents as preferred first-line therapy, and investigators have identified incorrect dosing and duration patterns that could lead to the development of antibiotic resistance to quinolones," Dr. File said at an international conference on community-acquired pneumonia.

Outpatient fluoroquinolone therapy should be considered only for patients at increased risk for drug-resistant *Streptococcus pneumoniae*, including those with comorbid conditions such as diabetes, chronic inflammatory lung disease, liver or renal insufficiency, malignancy, or congestive heart failure, and for patients who have been treated recently with antibacterial agents, said Dr. File, chief of the infectious disease service with Summa Health System in Akron, Ohio.

Since their introduction in the mid-1980s, fluoroquinolones have gained popularity because of their broad-spectrum coverage and high serum levels attained with oral administration—as well as increasing antibiotic resistance among pathogens. The approved agents, including gatifloxacin, gemifloxacin, levofloxacin, and moxifloxacin, are especially valuable for treating lower respiratory tract infections, given the growing prevalence of multiresistant pneumococci, Dr. File noted at the conference, sponsored by the International Society of Chemotherapy.

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DR. FILE

"The respiratory fluoroquinolones make excellent choices for therapy of community-acquired pneumonia because of their intrinsic activity against the key pathogens, including drug-resistant *S. pneumoniae* and the atypical organisms, and because of their excellent bioavailability and ability to penetrate well into pulmonary sites of infection," he added. Another advantage is that the serum half-life is longer than that of other agents, including ciprofloxacin, allowing for once-daily dosing.

Numerous randomized trials have favored fluoroquinolones over standard therapy in terms of efficacy, and several have suggested that initial treatment with the respiratory fluoroquinolones can lead to a rapid clinical response, thus justifying shorter-course therapy for many patients and minimizing the possibility for noncompliance, Dr. File said.

For previously healthy outpatients with community-acquired pneumonia who have not received antimicrobial drugs within the prior 3 months, updated recommendations for empiric antimicrobial therapy suggest treatment with an extended-spectrum macrolide or doxycycline. For patients with comorbidities or recent antimicrobial therapy, therapeutic options include a respiratory fluoroquinolone, a ketolide alone in the absence of enteric gram-negative bacteria, or a combination of a β-lactam plus a macrolide, Dr. File said.

"Another possible option for outpatients with modifying factors is the use of parenteral intramuscular or intravenous ceftriaxone plus an oral macrolide or doxycycline," he noted.

For inpatient therapy in the general hospital ward, recommended initial therapy includes monotherapy with one of the respiratory fluoroquinolones or a β-lactam plus a macrolide or doxycycline. "In some patients who don't have severe disease and have no risk factors for drug resistant *S. pneumoniae* or gram-negative pathogens, parenteral azithromycin monotherapy may be considered," Dr. File said.

Initial treatment for patients in the ICU "who are more likely to be very ill and to have multiple risk factors for more resistant pathogens" should be more aggressive, covering for both atypical organisms and traditional bacterial pathogens. Combination therapy with a potent antipneumococcal β-lactam and an advanced macrolide or a respiratory fluoroquinolone is recommended when *Pseudomonas* infection is not a consideration, he noted.

"The role of the respiratory fluoroquinolones for severe community-acquired pneumonia patients in the intensive care unit has not been established, thus fluoroquinolone monotherapy is not recommended in these patients," Dr. File added.

In the presence of risk factors for P*seudomonas* infection, as with severe structural lung diseases, "therapy should include drugs that are effective against pneumococcus, *Pseudomonas,* and *Legionella*," he said.

Such therapies include an antipneumococcal, antipseudomonal β-lactam plus ciprofloxacin or levofloxacin; an antipneumococcal, antipseudomonal β-lactam plus an aminoglycoside and an intravenous macrolide or an intravenous macrolide or an intravenous antipneumococcal quinolone; or, for patients with penicillin allergy, aztreonam plus levofloxacin or aztreonam plus moxifloxacin or gatifloxacin, with or without an aminoglycoside. ■

Activated Protein C Seen as Underused in Sepsis, Pneumonia

BY DIANA MAHONEY
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MONTREAL — Recombinant human activated protein C can be a lifesaver for some of the sickest patients with community-acquired pneumonia, Gary E. Garber, M.D., said at an international conference on community-acquired pneumonia.

Yet despite evidence that the coagulation inhibitor reduces mortality in patients with severe sepsis and community-acquired pneumonia (CAP) as their infection source, clinicians have been slow to embrace activated protein C—or drotrecogin alfa (Xigris)—as an adjunctive therapy for this well-defined patient population, said Dr. Garber, head of the division of infectious diseases at the University of Ottawa and the Ottawa Hospital.

In the landmark 2001 Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial, activated protein C (APC) reduced mortality from severe sepsis by nearly 20% among the 850 patients who received the drug, compared with the 840 patients given the placebo (N. Engl. J. Med. 2001;344:699-709). The findings led to FDA approval of the drug for adult patients who have a high risk of death due to severe sepsis associated with acute organ dysfunction.

In a retrospective analysis of the investigation, Dr. Garber and his colleagues determined that more than 35% of the study participants had CAP as their infection source, and of these, 26% had *Streptococcus pneumoniae* identified as the pathogen (Crit. Care Med. 2005;33:952-61).

Those CAP patients treated with APC had a 28% relative reduction in mortality, compared with those who received placebo. In patients with confirmed *S. pneumoniae* infections, "mortality fell from an absolute mortality of 32.9% to 20% with APC treatment," representing about a 40% relative reduction in mortality, he said.

'It is not that difficult to determine which patients should be treated with APC. Patients with pneumonia and systemic inflammation clearly benefit.'

The drug also had a significant effect on morbidity: Treated patients experienced faster resolution of cardiovascular and respiratory dysfunction and had more vasopressor- and ventilator-free days alive, compared with placebo patients, Dr. Garber said.

Because of its anticoagulant properties, APC is associated with an increased risk of serious bleeding, especially for patients with a preexisting risk for bleeding, such as those with central nervous system lesions or severe thrombocytopenia. This risk is one of the psychological barriers to wider usage of the drug, he noted.

In the PROWESS trial, 3.5% of the treated patients experienced bleeding-related complications, compared with 2% of patients on placebo. In both the treatment and placebo groups, the bleeding was usually related to an invasive procedure. However, Dr. Garber pointed out that "bleeding is a major risk associated with severe sepsis. If monitored, it is easily managed and is not a contraindication to using APC."

The drug is contraindicated in situations in which bleeding cannot be easily monitored; in patients with intracranial trauma or increased intracranial pressure; and in those who have had a recent epidural catheter, he said.

"In reality, when weighed against the benefit of keeping these patients alive, the slightly increased bleeding risk becomes less relevant," Dr. Garber said at the conference, which was sponsored by the International Society of Chemotherapy. Uncertainties about patient selection and drug cost are also barriers to clinician acceptance of APC, although neither concern is scientifically supported, he said.

"It is not that difficult to determine which patients should be treated with APC. Patients with pneumonia and systemic inflammation clearly benefit," he said, alluding to the retrospective PROWESS analysis; these data indicated that levels of interleukin-6—a strong negative prognostic marker in sepsis—dropped rapidly with APC treatment in septic CAP patients.

Specifically, "patients admitted to the [intensive care unit] with community-acquired pneumonia who require ventilatory and inotropic support will likely benefit from adjunctive treatment," Dr. Garber said. "These patients are at high risk of death, and experience tells us that the relative benefit of APC increases with increased mortality [risk] and severity of underlying coagulopathy and inflammation."

In terms of cost, a therapeutic course of APC in prototypic CAP patients with severe sepsis is more than twice that of tissue plasminogen activator (TPA), but it can save 6 out of every 100 lives, compared with 1 in 1,000 for TPA. "Instead of debating the role of APC in severe sepsis, we should be asking why TPA is the standard of care," he said.

Other obstacles to acceptance of APC include a poor understanding of and lack of standardized treatment protocols for sepsis, particularly severe sepsis, the condition for which the drug is approved, Dr. Garber hypothesized. He has served as an advisor for the drug's manufacturer, Eli Lilly & Co.

Perceived barriers notwithstanding, "in well-defined patient populations like CAP in the intensive care unit, APC should, without question, become a regular part of our treatment strategies," he said.

Toward this end, clinicians need to be better educated ion the management of severe sepsis in community-acquired pneumonia, Dr. Garber said. ■