PAH Guidelines Reflect Data on Newest Drugs

BY NANCY WALSH
New York Bureau

The American College of Chest Physicians has issued updated clinical practice guidelines for the medical management of pulmonary arterial hypertension that reflect findings from several recent clinical trials as well as the additional drugs that have been approved since the previous guidelines were issued in 2004.

The guidelines include an evidence-based, updated treatment algorithm intended to assist physicians in decision making, as "the paradigm for treatment of pulmonary arterial hypertension (PAH) continues to advance rapidly" (Chest 2007;131:1917-28).

Two studies that demonstrated survival benefits in patients treated with bosentan, which binds to both endothelin receptors (ET_A and ET_B) provided new data, said lead author Dr. David B. Badesch of the University of Colorado Health Sciences Center, Denver.

In the first study, 169 patients (aged between 13 and 80 years) with class III or IV PAH were treated with bosentan as first-line therapy. Survival was 96% at 12 months and 89% at 24 months, in contrast to predicted survival rates from the earlier National Institutes of Health registry of 69% and 57%, respectively (Eur. Respir. J. 2005;25:244-9).

In the second study, survival in 139 patients treated with bosentan was compared with historical data from 346 patients who had been treated with epoprostenol. Survival estimates after 1 and 2 years were 97% and 91%, respectively, in the bosentan-treated group, and 91% and 84% in the epoprostenol-treated group (Thorax 2005;60:1025-30).

Bosentan also has now been evaluated in children with PAH associated with congenital heart disease or connective tissue disease. In a retrospective study, 86 children were treated with bosentan with or without concomitant epoprostenol or treprostinil. WHO functional class improved in 46% of patients and was unchanged in 44%, and survival estimates at 1 and 2 years were 98% and 91% (J. Am. Coll. Cardiol. 2005;46:697-704).

Another recent study included 245 patients (ranging in age from 12 years to 78 years) who received bosentan, placebo, or one of two doses of a selective ET_A endothelin receptor antagonist, sitaxsentan. At week 18, patients receiving the higher dose of sitaxsentan (100 mg/day) had significant improvements on a 6-minute walk test, compared with those receiving placebo. The incidence of elevated transaminases was 6% in the placebo group, 5% in the sitaxsentan low-dose (50 mg/day) group, 3% in the high-dose sitaxsentan group, and 11% in the bosentan group (J. Am. Coll. Cardiol. 2006;47:2049-56).

Sitaxsentan remains investigational in the United States, but has been approved for use in Europe and Canada.

A second selective ET_A endothelin receptor antagonist, ambrisentan, was evaluated in a double-blind, dose-ranging study that included 64 adult patients with PAH. They were randomized to receive 1 mg, 2.5 mg, 5 mg, or 10 mg of ambrisentan orally once daily for 12 weeks. The 6-minute walk test improved significantly for all groups, with a mean increase from baseline of 36.1 meters. Improvements also were seen in WHO functional class, Borg dyspnea index, and cardiac index (J. Am. Coll. Cardiol. 2005;46:529-35).

This drug was recently approved for class II and class III PAH in the United States.

The phosphodiesterase inhibitor sildenafil also is now approved for the treatment of all classes of PAH in a dosage of 20 mg three times daily. The drug was evaluated in a double-blind study that randomized 278 patients (mean age 50 years) to placebo or 20, 40, or 80 mg three times daily for 12 weeks.

In summarizing the treatment options, the authors noted that for patients in functional class II, the only current recommended drugs are sildenafil and subcutaneous and intravenous treprostinil, and suggested that sildenafil may be the first choice for most patients because of ease of administration and relative efficacy.

For patients in functional class III, five drugs are available: bosentan, sildenafil, intravenous epoprostenol, inhaled iloprost, and subcutaneous or intravenous treprostinil. For those with early class III disease, oral bosentan or sildenafil may be used, with the choice reflecting relative toxicities. For patients with more advanced disease, prostanoid therapy may be needed.

All the available agents are approved for patients with class IV PAH. However, the authors wrote, "[we] strongly encourage IV epoprostenol as the treatment of choice for these most critically ill patients. IV epoprostenol has a rapid and predictable onset of action, and most experts are familiar with how to titrate this drug in the acute setting."

In conclusion, they also strongly recommended that patients with PAH be referred to specialized centers because of the complexity of the diagnostic and therapeutic considerations involved. ■

CLINICAL GUIDELINES FOR FAMILY PHYSICIANS

Bronchiolitis in Children: Birth to 2 Years

BY NEIL S. SKOLNIK, M.D., AND KELLY L. GANNON, D.O.

The American Academy of Pediatrics, with support from the American Academy of Family Physicians (AAFP), the Agency for Healthcare Research and Quality (AHRQ), the American Thoracic Society, the American College of Chest Physicians, and the European Respiratory Society, assembled a subcommittee on diagnosis and management of bronchiolitis, which developed recommendations for the prevention, diagnosis, and treatment of bronchiolitis (Pediatrics 2006;118;1774-93).

Guidelines are most useful when they are available at the point of care. A concise yet complete handheld computer version of this guideline is available for download, compliments of FAMILY PRACTICE NEWS, *at www.redi-reference.com.*

Epidemiology

Bronchiolitis in infants is most commonly caused by viral infection of the lower respiratory tract. The predominant pathogen is the respiratory syncytial virus (RSV). In the United States, the peak incidence of RSV occurs between November and March.

Prevention

Hand hygiene is important in the prevention of nosocomial RSV spread. Alcohol-based solutions are most effective, with antimicrobial soap a reasonable alternative. Personnel and family members should also be instructed on proper hand sanitation. Providers should recommend that infants not be exposed to passive smoke. Breast-feeding should be encouraged.

Palivizumab may be administered for selected infants and children younger than 24 months with chronic lung disease of prematurity, or a history of prematurity (defined as fewer than 35 weeks' gestation), or with congenital heart disease. Prophylaxis should be given in 5 monthly injections, usually beginning in November or December, at a quantity of 15 mg/kg intramuscularly per dose. Guidelines are available for prophylactic treatment.

Diagnosis

Bronchiolitis is a clinical diagnosis that does not require laboratory or radiologic testing. It is characterized by acute inflammation, edema, and necrosis of the epithelial cells lining small airways; increased mucus production; and bronchospasm. Signs and symptoms are typically rhinitis, tachypnea, wheezing, coughing, crackles, retractions, and/or nasal flaring. At the time of diagnosis, the patient should be assessed for hydration and specific risk factors for severe disease, which are important when deciding on management and further evaluation. The risk factors include age younger than 12 weeks, underlying cardiopulmonary disease, immunodeficiency, or a history of prematurity.

Treatment

Patients admitted to the hospital primarily benefit from oxygen, attention to hydration, supportive care, and monitoring for deterioration. Routine use of bronchodilators, corticosteroids, antivirals, and chest physiotherapy is not recommended. A carefully monitored trial of α-adrenergic or β-adrenergic medication is an option, with nebulized epinephrine being preferred over albuterol for inpatients. Continue bronchodilator therapy if there is a documented positive clinical response to the medication. An objective evaluation of response should be used. Most positive studies of bronchodilators for the management of bronchiolitis show transient improvement in some children, which is of unclear clinical significance. Corticosteroids have been evaluated in multiple trials, and there does not seem to be a significant benefit to corticosteroid therapy in individual studies or in aggregate meta-analysis of results.

Ribavirin has only marginal benefit, is expensive, and has potential health risks for personnel involved in the child's care. It should be considered only in selected patients with documented RSV infection who have severe disease, or who are at risk for severe disease by being immunocompromised or having severe cardiopulmonary disease.

Antibiotics are not effective against viral infections and so should be used in children with bronchiolitis only when there is a specific indication of the coexistence of a bacterial infection.

Although 25% of infants with bronchiolitis have an infiltrate on chest x-ray, very few without frank consolidate have a bacterial pneumonia. About 50% of patients have evidence of otitis media, with bacteria growing out in studies on tympanocentesis. Otitis media in the setting of bronchiolitis should be treated as if bronchiolitis were not there.

Supplemental oxygen should be used if the pulse oximetry declines persistently below 90% in previously healthy children. Oxygen should be titrated to maintain the patient's SpO_2 at or above 90%, and may be discontinued if the SpO_2 is at or above 90% and the infant is feeding well and has minimal respiratory distress.

As the clinical course improves, the continuous measurement of SpO_2 is not routinely necessary. Premature infants and those with underlying cardiopulmonary disease should be monitored closely.

The Bottom Line

Patients admitted to the hospital primarily benefit from oxygen, attention to hydration, supportive care, and monitoring for deterioration. The routine use of bronchodilators, corticosteroids, antivirals, and chest physiotherapy is not recommended.

DR. SKOLNIK is an associate director of the family Medicine Residency Program at Abington (Pa.) Memorial Hospital and a coauthor of "Redi-Reference Clinical Guidelines." DR. GANNON is a third-year family medicine resident at Abington.