Apply Golden Hour Rule in Pediatric Septic Shock

Each additional hour of persistent shock from the time of diagnosis doubles the risk of death.

BY PATRICE WENDLING

FROM THE PEDIATRIC HOSPITAL MEDICINE 2010 MEETING

MINNEAPOLIS – Clinicians often hesitate to call a case of pediatric septic shock, even though they may treat the patient appropriately, according to one critical care physician.

Dr. Jerry McLaughlin presented the case of an alert but ill-appearing 1-year-old with 2 days of fever and vomiting, negative chest x-ray, abnormal urine analysis, capillary refill time of 3 seconds, cool extremities, and a normal respiratory rate, blood pressure, and urine output.

When he asked who would call this case septic shock, only one hand rose up among roughly 75 physicians attending the session at the Pediatric Hospital Medicine 2010 meeting.

"We see patients who look like this all the time, and you don't want to say shock – shock is somebody who's clearly obtunded and needs the ICU and is falling apart – that is not this patient, but she meets criteria and she needs to be treated accordingly," Dr. McLaughlin said. "The thing is that many of you would treat her appropriately in the first hour and her symptoms would reverse, but you just would never call it. I say this because we need to be speaking the same language."

Recognition Gap

Although the term "shock" carries with it a certain amount of baggage for medical professionals and families, part of the problem lies in recognition, said Dr. McLaughlin of the department of critical care medicine at Seattle Children's Hospital. He cited a study of 91 infants and children who presented to local community hospitals with septic shock that found community physicians achieved shock reversal in just 26% of patients, and used resuscitation practices consistent with American College of Critical Care Medicine–Pediatric Advanced Life Support (ACCM-PALS) septic shock guidelines in 30% (Pediatrics 2003;112:793-9).

A quick quiz about pediatric sepsis facts at the meeting also suggested some knowledge gaps, with Dr. McLaughlin eliciting an audible gasp when he said that 10 times as many infants develop sepsis compared with older children, and that 10% of the 47,000 pediatric sepsis cases reported each year end in death.

Timing, Timing, Timing

International definitions for sepsis and organ dysfunction have been developed by an expert panel, but many attendees seemed unaware of the specific criteria for each diagnosis on the sepsis continuum (Pediatr. Crit. Care Med. 2005;6:2-8). Still others suggested that the panel's broad definition of sepsis – systemic inflammatory response syndrome (SIRS) plus infection – would encompass a disproportionate number of infants and children in the emergency department.

Just as there are "golden hours" in the treatment of stroke and acute MI, early recognition of septic shock and formulation of a goal-directed therapeutic plan is critical, Dr. McLaughlin stressed at the meeting sponsored by the Society of Hospital Medicine, American Academy of Pediatrics, and Academic Pediatric Association. In the community hospital study, each additional hour of persistent shock from the time of diagnosis was associated with a doubling of the risk of death.

The good news is that physicians don't have to come up with their own plan, but have the 2007 ACCM guidelines, published last year (Crit. Care Med. 2009;37:666-88) to direct their therapies. The five elements central to early management are oxygen, vascular access, fluids, inotropes, and antibiotics.

"If a patient comes in with septic shock and it's clear, don't delay getting labs to do this stuff," he said. "You all know how long it can take to get a CBC and blood work. Suddenly 40 minutes has passed and the nurses are saying they can't get blood, and that's 40 minutes lost."

Oxygen delivery is pretty straightforward, with the method typically dependent on patient preference. Access can be achieved intravenously or via an intraosseous line, which is often quicker to achieve.

Fluid therapy is an entirely different matter, with the optimal amount of fluid debated because of concerns that excess fluid can induce pulmonary edema or heart failure in children with septic shock.

"Some people say 20 mL/kg, some say 60 [mL/kg] because that is what the guidelines say, but I can tell you that by the time some of these kids leave me they've already had 200 mL/kg or more," he said. "You give as much as the patient needs and don't hold back because of fear. If you hold back on fluid, you push up mortality."

Tackling the Fluid Therapy Question

An audience member said there may be an exception, as research suggests that pushing fluids may actually increase mortality in children who are severely malnourished. Dr. McLaughlin responded that some of the best literature on fluid resuscitation has been published by Dr. Cláudio Oliveira's group in Brazil, a country that has a significant amount of malnutrition and reports higher survival rates in patients receiving early, adequate fluid therapy (Pediatr. Emerg. Care 2008;24:810-5).

The type of fluid solution does not seem to influence the ability of fluids to improve perfusion, organ function, and outcome. Dr. McLaughlin recommended using normal saline or lactated Ringer's solution instead of 5% albumin, which has not been shown to be decidedly better than saline.

Titrate to Symptoms

The important point to remember is to titrate to effect, he said. This means that the patient's feet and hands should get warmer, his blood pressure should come up, his heart rate should go down, and his capillary refill time should be more normal – although not necessarily faster or slower because some kids have a really brisk capillary refill rate, he said. Clinicians also should titrate to symptoms, which involves feeling a patient's liver.

"If you're giving fluids to the point you're getting hepatomegaly, then you've probably reached your fluid limit for that patient," Dr. McLaughlin said. "If you're getting more tachycardia as you give more fluids, that should cause you to pause and … shift your therapy."

Various inotropes can be used for septic shock, and Dr. McLaughlin recommended that clinicians use the one they are most familiar with. In the general pediatric population, that typically means starting out with dopamine and epinephrine, he said, adding that dobutamine and milrinone "could get you into trouble."

Antibiotic therapy should address the specific epidemiology of the patient population: ceftriaxone for community-acquired pediatric sepsis; ampicillin with gentamicin or cefotaxime, or cefotaxime for neonates; and ceftazidime with or without vancomycin for patients with neutropenia and central venous access.

"What I see too many times is that patients get assessed, plans get started, and then for an hour and a half no one's gone back to look at that kid again," Dr. McLaughlin said. "That's not okay. You have to stay on top of these kids because time matters. An hour matters."

He observed that hospitalists are in a unique position to affect sepsis outcomes because they have early access to patients. He also pointed out that 50% of patients with sepsis have chronic disease, SIRS is present in 7% of hospitalized patients, and sepsis is a quality indicator. ■

Ceftaroline Active Against *S. pneumoniae*, MRSA, and MSSA

BY BRUCE JANCIN

FROM THE EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

VIENNA – Ceftaroline, an investigational fifth-generation cephalosporin in late-stage development, is likely to become a major drug in the treatment of infections caused by *Staphylococcus aureus* and *Streptococcus pneumoniae,* including the strains resistant to current widely prescribed antimicrobials.

Ceftaroline exhibited impressive in vitro activity in standardized antimicrobial susceptibility testing involving 8,842 isolates of methicillin-resistant *S. aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA) from 56 U.S. and European medical centers during 2008-2009, Dr. Helio S. Sader reported at the meeting.

In a separate laboratory study presented at the congress, Dr. Michael R. Jacobs reported that ceftaroline showed more in vitro activity against the prevailing U.S. pediatric and adult serotypes of *S. pneumoniae* than any of the other 13 agents tested.

The investigational drug's performance was particularly strong against the isolates from pediatric patients, which tend to be among the most resistant to currently available antimicrobials. Indeed, the often multidrug-resistant serotype 19A accounted for 32.6% of all *S. pneumoniae* isolates from pediatric patients, compared with 15% in adults.

Ceftaroline had a minimum inhibitory concentration (MIC) 90 of 0.25 mcg/mL against serotype 19A, compared with 65.6 mcg/mL for ceftriaxone. The MIC90s for 12 other currently marketed antimicrobials ranged from 13.8 to 100 mcg/mL, noted Dr. Jacobs, professor of clinical microbiology at Case Western Reserve University, Cleveland.

The study included 891 *S. pneumoniae* isolates that were obtained from patients in 22 U.S. cities in 2008. The isolates came from infections at all body sites, and one-third were from pediatric patients. Pediatric isolates were significantly less susceptible to amoxicillin, penicillin, and ceftriaxone than were adult isolates. Serotypes covered in the seven-valent pneumococcal conjugate vaccine were uncommon in both adults and children.

Ceftaroline is now under Food and Drug Administration review for two potential indications: community-acquired pneumonia and complicated skin and skin structure infections.

In the *S. aureus* study, ceftaroline was 16-fold more active than was ceftriaxone against MSSA strains. It also showed strong potency against MRSA strains, with MIC90s of 1-2 mg/L, making it at least 64-fold more potent than ceftriaxone, according to Dr. Sader of JMI Laboratories, North Liberty, Iowa.

He drew particular attention to the investigational agent's outstanding performance against MRSA isolates with SCCmec type IV, which is found in the U.S. pandemic community-associated MRSA clone USA300, as well as in several problematic clones circulating in Europe. Ceftaroline's MIC90 of 1 mg/L against these isolates was the most favorable of the 10 drugs tested.

Ceftaroline is being developed by Forest Laboratories, which supported both studies. ■