Pharmacological Management of Pediatric Patients With Sepsis

Marroyln L. Simmons, PharmD, MS, BCPS
Spencer H. Durham, PharmD, BCPS
Chenita W. Carter, PharmD

ABSTRACT

With an overall mortality rate of 4.2%, sepsis is one of the most common causes of death in children worldwide. The Surviving Sepsis Campaign outlines rapid initiation of volume resuscitation with crystalloids and timely administration of broad-spectrum antibiotics as the backbone of sepsis treatment. Initial antibiotics should be broad enough to cover the most likely pathogens, but antibiotic therapy should be de-escalated when culture results become available. Therapy with a vasopressor and/or an inotrope is often necessary in patients with sepsis to improve blood pressure and cardiac output. Adjunctive therapy with hydrocortisone is sometimes beneficial in the setting of catecholamine resistance and/or adrenal insufficiency. Insulin may also be needed in some patients for the treatment of hyperglycemia. Current guidelines have improved the treatment of sepsis, but more research is needed. This article reviews sepsis pathophysiology, treatment, and supportive care specifically as they relate to pediatric patients.

Keywords: broad-spectrum antibiotics, cardiovascular support, pediatrics, sepsis

Sepsis is one of the most common causes of death in children worldwide. Odetola and colleagues conducted a retrospective study in 2003 that identified 13,000 hospitalizations for severe sepsis. This study provided a national estimate of 21,448 severe sepsis admissions, with an overall mortality rate of 4.2%. This number underscores the public health magnitude and importance of this condition. Although much progress has been made in the recognition and treatment of sepsis, it continues to be an important and critical issue in the pediatric population.

The American College of Critical Care Medicine published “Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Patients in Septic Shock,” which calls for a stepwise approach in the management of septic shock. These guidelines recommend screening for high-risk patients, obtaining bacterial cultures when the patient arrives at the hospital, initiating broad-spectrum antibiotic therapy, identifying and controlling the source of infection, intravenously administering fluids, and maintaining glycemic control. These guidelines have been shown to decrease hospital mortality rates due to sepsis. Patients should be assessed rapidly, and goal-directed therapy should be initiated within the first hour they arrive at the hospital to decrease mortality rate. The purpose of this article is to review sepsis specifically in the pediatric population.
give a brief overview of pathophysiology, define sepsis as it relates to pediatrics, and review the treatment and supportive care of patients with sepsis. Neonatal sepsis is not discussed, as it is beyond the scope of this article.

Definition and Pathogenesis
In the past, the term *sepsis* has been used to describe a wide range of clinical syndromes, which led to much confusion among clinicians. To provide a more standardized definition, the American College of Chest Physicians and the Society of Critical Care Medicine attempted to standardize the term *sepsis* as well as other related terms to provide a more concise definition, which led to the creation of the term *systemic inflammatory response syndrome* (SIRS), which is a general description of widespread inflammation that may be due to an infectious or noninfectious cause.

In 2007, the International Pediatric Sepsis Consensus Conference modified the adult SIRS criteria and associated definitions for pediatric patients (see Table 1). Sepsis, as defined by Goldstein et al., is SIRS in the presence of or as a result of a suspected or proven infection. *Septic shock* is defined as sepsis with hypotension, despite fluid resuscitation. Sepsis is a multifactorial process activated by the inflammatory cascade and mediated by hormones, cytokines, and enzymes. It can be categorized by hypothermia or hyperthermia, tachycardia, tachypnea, weak peripheral pulses, lactic acidosis, decreased urine output, wide pulse pressures, delayed capillary refill, and hypotension, ultimately progressing to cardiovascular collapse. Other clinical symptoms can include irritability, lethargy, confusion, and oliguria.

### Causes of Sepsis
Sepsis can be caused by almost any type of microorganism, including bacteria, viruses, fungi, protozoa, spirochetes, and rickettsiae. Bacteria, however, cause an overwhelming majority of cases (>90%). Sepsis can be caused by so many different types of bacteria that empiric therapy is not generally directed at only a few pathogens, but at many different ones.

### Table 1: Definition of Sepsis and Related Terms

| SIRS (systemic inflammatory response syndrome): The presence of at least 2 of the following conditions (one of which must include abnormal temperature or leukocyte count): |
| Core temperature > 38.5°C or < 36°C |
| Tachycardia or bradycardia |
| Mean respiratory rate > 2 standard deviations above normal for age or mechanical ventilation for an acute process that is not attributed to an underlying neuromuscular disease or general anesthesia |
| Leukocyte count elevated or decreased for age (not secondary to chemotherapy-induced leukopenia) or the presence of > 10% immature neutrophils |

| Infection (evidence includes positive findings on clinical examination, imaging, or laboratory tests) |
| A suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen |

Or

A clinical syndrome associated with a high probability of infection

**Sepsis**

SIRS in the presence of or as a result of a suspected or proven infection

**Severe sepsis**

Sepsis and one of the following:

- Cardiovascular organ dysfunction
- Acute respiratory distress syndrome
- Two or more organ dysfunctions (respiratory, renal, neurological, hepatic, hematologic)

**Septic shock**

Sepsis and cardiovascular failure
Patients typically develop sepsis from a primary site of infection, such as the lung, bloodstream, urinary tract, intra-abdominal cavity, or skin and soft tissue. If the primary site of infection is known when a patient presents with sepsis, antimicrobial therapy should be directed at the pathogens most likely to arise from the primary site. However, the primary site of infection is often not known when the patient first presents. Because bacteria are the most common causes of pediatric sepsis, this article focuses on bacterial causes and treatments.

Since the late 1980s, gram-positive organisms have become the leading cause of sepsis in all patients, accounting for more than 50% of cases. The most common gram-positive organisms involved include *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Staphylococcus epidermidis* and other coagulase-negative staphylococci, and *Enterococcus* species. Note that antimicrobial resistance to these pathogens has been steadily increasing in recent years, as seen in the increasing incidence of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus*. Sepsis caused by coagulase-negative staphylococci is most commonly associated with central catheter infections and infected intravascular devices, such as mechanical heart valves. Prolonged hospitalization and treatment with broad-spectrum cephalosporin agents increase the risk of sepsis caused by *Enterococcus* species.

Although gram-negative organisms cause sepsis slightly less frequently than do gram-positive organisms, sepsis caused by gram-negative organisms is typically more severe, with an overall higher mortality rate. Gram-negative organisms are more likely to cause septic shock than are gram-positive organisms, and gram-negative bacteremia is more likely to progress to clinical sepsis. The most common gram-negative organism implicated in sepsis is *Escherichia coli*. Other potential bacteria that can cause sepsis include species of *Klebsiella*, *Pseudomonas*, *Proteus*, *Serratia*, and *Enterobacter*. Many gram-negative species, such as *Pseudomonas* and *Enterobacter*, have become increasingly resistant to antimicrobial therapy. *Pseudomonas aeruginosa*, a common cause of infections in immunocompromised and neutropenic patients, is responsible for more sepsis-related mortality than any other organism.

Obligate anaerobes, such as *Bacteroides fragilis*, are infrequent causes of sepsis, although they can be implicated in polymicrobial infections. Obligate anaerobes are normal flora of the gastrointestinal tract, so they may cause sepsis if the gastrointestinal tract is the primary site of infection. As mentioned previously, sepsis caused by fungal infections is not common, accounting for only about 5% of all cases. However, note that between the years 1979 and 2000, the incidence of fungal sepsis increased by 200%. *Candida albicans* is the most commonly implicated agent in sepsis, but other species, such as *Candida glabrata*, have also become important pathogens. Risk factors for fungal sepsis include treatment with broad-spectrum antibiotics, prolonged hospitalization, placement of a central venous catheter, and underlying immunosuppression.

### Treatment of Sepsis

#### Vascular Access in Patients With Sepsis

Rapid administration of antibiotics, fluids, and vasopressors is of utmost importance in the treatment of sepsis. Central venous access is the preferred type of vascular access, but intravenous (IO) access should be established if reliable vascular access cannot be obtained rapidly. The 2007 update of the clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock states that in patients who do not respond to initial fluid resuscitation, a peripheral inotrope such as low-dose dopamine or epinephrine may be started in a second peripheral IV or through a second IO if available. If an inotrope is started through a peripheral IV or an IO, the inotrope should be diluted for peripheral administration; alternatively, a second carrier solution, running at a flow that will ensure the inotrope reaches the heart in a timely fashion, can be used. These medications can significantly affect tissue if infiltration occurs; therefore, the dosage of the inotrope should be reduced if signs of peripheral infiltration or ischemia are noted. Central venous access should be established as quickly as possible, and a central inotrope such as epinephrine or dopamine should be started. When the patient shows the effects of the infusion, the use of the peripheral inotrope may be discontinued.

#### Fluid Resuscitation

In pediatric patients, a classic symptom of septic shock is severe hypovolemia. Approximately 50% of children will present with cold
extremities, low cardiac output, and elevated systemic vascular resistance (SVR). In children, hypotension is often a late consequence of shock as a result of the increase in SVR. In addition to these findings, oxygen supply to the tissues is often inadequate. Early goals of therapy should be to restore intravascular blood volume and maintain blood flow to essential organs.

The Surviving Sepsis Campaign recommends that initial fluid resuscitation should be instituted using bolus infusions of crystalloids (eg, 0.9% sodium chloride or lactated ringers). These guidelines suggest doses of 20 mL/kg over 5 to 10 minutes. In sepsis, a large fluid deficit is often present and doses of 40 to 60 mL/kg of crystalloid are frequently required, but much higher doses have been used. Patients should be monitored for signs of improvement, including heart rate, urine output, capillary refill, level of consciousness, adequacy of blood pressure, quality of peripheral pulses, and temperature.

Colloids (eg, albumin, gelatins, dextrans, and hydroxyethylstarch solutions) are an alternative for fluid resuscitation. Unlike crystalloids that pass easily through the endothelial barrier and persist in the intravascular space for only short periods of time, colloids are larger molecules and do not readily cross semipermeable membranes, which allows them to maintain plasma oncotic pressure better and remain in the intravascular space longer. However, in septic shock, membrane permeability increases, which decreases the intravascular persistence of colloids. No evidence supports the superiority of colloids or crystalloids for use in fluid resuscitation. Crystalloids are supported as first-line treatment because of their ready availability and lower cost. However, some adult literature supports the use of albumin in severely ill patients with hypoalbuminemia.

Principles of Antimicrobial Therapy

One of the fundamental principles in the treatment of pediatric sepsis is the prompt initiation of appropriate, broad-spectrum antibiotics. Several studies have demonstrated that the early administration of appropriate antibiotics decreases the mortality rate in patients with sepsis. The 2008 Surviving Sepsis Campaign highlights several recommendations for the use of antimicrobials in the treatment of sepsis (see Table 2).

One of the most important recommendations is that IV antibiotics should be initiated as promptly as possible, but always within the first hour of a patient presenting with sepsis. Each hour of therapy delay causes a corresponding increase in mortality rate. Blood cultures, as well as other cultures that may be applicable to the specific case, should be obtained prior to the initiation of antibiotics as long as obtaining the cultures does not significantly delay the administration of antibiotics. At least 2 blood cultures should be obtained, one of which should be percutaneous. In addition, cultures should be obtained from each vascular access device that has been in place for more than 48 hours, such as a peripherally inserted central catheter or a port. Obtaining blood cultures is essential to confirm the presence of infection, as well as to allow for de-escalation of antibiotics. Other studies such as chest x-ray films and cerebrospinal fluid cultures may be useful in determining the primary site of infection.

In general, the initial antibiotic(s) should be broad enough to cover the most likely pathogens, as well as have adequate tissue penetration into the presumed primary source of infection. Clinicians should be aware of specific susceptibility patterns in their institution as well as their community setting to help guide initial therapy. For example, if the specific institution has a high prevalence of MRSA, the clinician should consider beginning empiric coverage of this pathogen. Clinicians must also be cognizant of the risk of fungal sepsis. If there is a reasonable possibility that the patient is experiencing a fungal infection, therapy with an appropriate antifungal agent should be initiated. If the patient is at risk for or appears to be infected with a gram-negative bacterium, the clinician may need to initiate treatment with 2 antibiotics with different pharmacological mechanisms of action; this process is often referred to as combination therapy or “double covering.” Combination

---

**Table 2: Possible Empiric Antibiotic Combinations for Pediatric Sepsis**

<table>
<thead>
<tr>
<th>Antibiotic Combination</th>
<th>Pathogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended-spectrum penicillin ± aminoglycoside ± vancomycin</td>
<td>Pseudomonas, Enterococcus</td>
</tr>
<tr>
<td>Third- or fourth-generation cephalosporin ± aminoglycoside ± vancomycin</td>
<td>MRSA</td>
</tr>
<tr>
<td>Carbapenem ± aminoglycoside ± vancomycin</td>
<td>Carbapenem-resistant strains of Enterobacteriaceae</td>
</tr>
</tbody>
</table>

A fluoroquinolone may be substituted for an aminoglycoside in any of the above regimens.

The third-generation cephalosporin ceftriaxone should not be used when *Pseudomonas* is suspected or proven.
therapy is useful if a patient has febrile neutro-
penia or has a proven or suspected infection as a re-
sult of *Pseudomonas* species. Note that, while often used in clinical practice, combina-
tion therapy has not been well studied in clinical
trials. Despite the possible need for initial empiric combination therapy, it should gen-
erally not be continued for more than 3 to 5 days
if the infecting pathogen and susceptibility
results are known. The total length of therapy
for treatment of sepsis should be limited to 7 to
10 days. However, longer treatment durations
may be necessary if the patient has a slow clini-
cal response or immunologic deficiencies, such
as neutropenia, or if the source of infection is
undrainable.13

The Surviving Sepsis Campaign guidelines
further suggest that antimicrobial therapy
should be reevaluated on a daily basis to opti-
mize efficacy, avoid toxicities associated
with antibiotic therapy, and minimize costs.
Although blood cultures may be negative in
more than 50% of all sepsis cases, antimicro-
bial therapy should be tailored to the specific
pathogen if one is able to be identified.13 A
general rule for selecting an antibiotic for a
specific pathogen is that the lowest-spectrum
agent should be selected, provided it will be as
effective in killing the organism as a broader-
spectrum agent.

For sepsis, antimicrobial agents that are bac-
tericidal are generally preferred over bacterio-
static agents. Bacteriostatic antimicrobials, such
as linezolid or clindamycin, will inhibit growth
of the organism but must rely on the patient’s
own immune system to completely remove the
bacteria from the body. In contrast, bactericidal
agents, such as the β-lactams, will destroy the
bacteria without contribution from the immune
system.18 Narrowing the antibiotic spectrum, as
well as limiting the duration of antibiotic ther-
apy, is essential to prevent the development of
antimicrobial resistance. In addition, this prac-
tice decreases the risk of development of a
superinfection with highly resistant organisms,
such as vancomycin-resistant *Enterococcus*.

As discussed previously, no specific guide-
lines are available as to what antibiotics to
begin as empiric therapy in patients with seps-
is. Some possible combinations are shown in
Table 2. The most common classes of antibiot-
ics to be used in the empiric treatment of sepsis
include β-lactams, aminoglycosides, fluoroqui-
nolones, and vancomycin. Because these agents
are so commonly used, a review of their prop-
erties is warranted. Dosing of these agents is
provided in Table 3.

β-Lactams
The β-lactam class of antibiotics consists of all
the penicillin, cephalosporin, and carbapenem
antimicrobial agents. β-Lactams display their
mechanism of action by inhibiting cell wall syn-
thesis, which results in bactericidal killing of
susceptible organisms. They manifest their anti-
microbial activity in a time-dependent manner,
indicating that efficacy is determined by the
amount of time serum drug concentrations
remain above the minimum-inhibitory concen-
tration of the pathogen. β-Lactams used in the
treatment of sepsis have broad activity against
both gram-positive and gram-negative bacteria,
and some are active against obligate anaerobes.
However, they do not have activity against
MRSA. Clinicians prefer β-lactam drugs for the
treatment of sepsis because of their relatively
benign adverse effect profile. The most con-
cerning of the adverse effects of these agents is
hypersensitivity reactions. However, if a patient
experiences hypersensitivity to a β-lactam,
another β-lactam from a different family can be
used, as cross-reactivity between the families,
though possible, is uncommon (< 10%).18

The most commonly used members of the
penicillin family for the treatment of sepsis are
the extended-spectrum agents piperacillin/
tazobactam, and ticarcillin/clavulanate. For
these formulations, the penicillins piperacillin
and ticarcillin are combined with the
β-lactamase inhibitors tazobactam and clavu-
lanate, respectively. β-Lactamases are enzymes
produced by some bacteria that will deactivate
certain β-lactam antibiotics; thus, combining a
β-lactam with a β-lactamase inhibitor greatly
increases the spectrum of activity of these
agents. Piperacillin/tazobactam and ticarcillin/
clavulanate are the principal penicillin combi-
nations used for the treatment of sepsis,
because they cover both gram-positive organ-
isms and gram-negative organisms, including
*Pseudomonas*, as well as obligate anaerobes.7,18

The most commonly used agents from the
cephalosporin family include the third-genera-
tion agents ceftriaxone, cefotaxime, and
ceftazidime and the fourth-generation agent
cefepime. Cefepime is the most broad spectrum
of the agents, with excellent activity against
many gram-positive and gram-negative organ-
isms, including *Pseudomonas*.5,18 Cefotaxime
and ceftriaxone have a virtually identical spectrum of activity. However, cefotaxime should be used preferentially in neonates as ceftriaxone can cause kernicterus and cannot be used with calcium-containing IV fluids. Many clinicians prefer to use ceftriaxone in nonneonates as it allows for once-daily dosing as compared with 3- to 4-times daily dosing with cefotaxime. Although both ceftriaxone and ceftazidime are third-generation cephalosporins, they differ in their spectrum of activity. Ceftriaxone, unlike ceftazidime, does not have activity against *Pseudomonas*. However, ceftazidime does not have any appreciable coverage of most gram-positive organisms, particularly *Streptococcus pneumoniae*, for which ceftriaxone is a common treatment. None of the cephalosporins used in the treatment of sepsis has any activity against obligate anaerobes or *Enterococcus*.¹⁸

The carbapenems are perhaps the most broad-spectrum antimicrobials available on the market today. Currently, 4 different agents are available: ertapenem, imipenem/cilastatin, meropenem, and doripenem. Doripenem, the newest carbapenem, has not been extensively studied in pediatric patients and so will not be discussed in this article. In adolescents and adults, ertapenem has the advantage of once-daily dosing, but in younger children it must be dosed every 12 hours. In addition, it does not cover *Pseudomonas*, so it is infrequently used for the treatment of sepsis.¹⁹ Imipenem/cilastatin and meropenem have excellent activity against gram-positive organisms, gram-negative organisms (including *Pseudomonas*), and obligate anaerobes. Imipenem is rapidly converted in the body by the enzyme dehydropeptidase to toxic metabolites. It is, therefore, always administered with cilastatin, a compound that blocks

<table>
<thead>
<tr>
<th>Antibiotic Class</th>
<th>Penicillins</th>
<th>Cephalosporins</th>
<th>Carbapenems</th>
<th>Aminoglycosides</th>
<th>Fluoroquinolones</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic</td>
<td>Piperacillin/tazobactam</td>
<td>Ceftriaxone</td>
<td>Meropenem</td>
<td>Gentamicin</td>
<td>Ciprofloxacin</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Dosage</td>
<td>300-400 mg/kg per day ÷ every 6-8 h</td>
<td>50-100 mg/kg per day ÷ every 12-24 h</td>
<td>20 mg/kg per dose every 8 h</td>
<td>2.5 mg/kg per dose every 8 h OR</td>
<td>20-30 mg/kg per day ÷ every 12h</td>
<td>15 mg/kg per dose every 6 h</td>
</tr>
<tr>
<td>Comments</td>
<td>Dosing is based on the penicillin component</td>
<td>Ceftriaxone and cefotaxime are not active against <em>Pseudomonas</em></td>
<td>Imipenem/cilastatin should be avoided in patients with or at risk for seizures</td>
<td>Dosing is the same for both agents</td>
<td>Because of black-box warning for tendon disorders, use of fluoroquinolones should be reserved for patients who cannot tolerate other agents or for resistant infections</td>
<td>Dosing should be adjusted to keep trough 15-20 mg/L for patients with sepsis</td>
</tr>
<tr>
<td>Citricillin/clavulanate</td>
<td>200-300 mg/kg per day ÷ every 4-6 h</td>
<td>Cefotaxime</td>
<td>Imipenem/cilastatin</td>
<td>Tobramycin</td>
<td>Levofloxacin</td>
<td></td>
</tr>
<tr>
<td>Dosage</td>
<td>100-200 mg/kg per day ÷ every 6-8 h</td>
<td>100-150 mg/kg per day ÷ every 8 h</td>
<td>60-100 mg/kg per dose ÷ every 6 h</td>
<td>5-7.5 mg/kg per dose once daily</td>
<td>10 mg/kg per dose every 12h (&lt;5 years old) and 10 mg/kg per dose once daily (≥5 years old)</td>
<td></td>
</tr>
<tr>
<td>Comments</td>
<td>The higher end of the dosing range is recommended for <em>Pseudomonas</em> infections</td>
<td>Cefepime should be given every 8 h in febrile neutropenic patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>50 mg/kg per dose every 8-12 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Antibiotic Dosing by Class

© 2012 American Association of Critical-Care Nurses. Unauthorized reproduction of this article is prohibited.
Aminoglycosides

Although several agents are in the aminoglycoside family of antibiotics, the most common drugs used clinically are gentamicin, tobramycin, and amikacin. The aminoglycosides work to disrupt bacterial protein synthesis in a bactericidal manner. Aminoglycosides provide broad activity against most gram-negative bacteria, including Pseudomonas. They are generally not used alone for the treatment of gram-positive infections but are sometimes combined with a β-lactam agent to produce a synergistic effect. They are not active against obligate anaerobes. In general, gentamicin and tobramycin should be used as first-line therapy. Amikacin may display activity against pathogens that are resistant to gentamicin and tobramycin, so its use should be reserved for cases of resistant infections.5,18

Although the aminoglycosides are highly useful agents for the treatment of sepsis, clinicians must be aware of important adverse effects, specifically nephrotoxicity and ototoxicity. All patients receiving aminoglycoside therapy should have baseline renal function assessed, and it should continue to be assessed periodically throughout treatment, at least weekly and possibly more frequently, depending on the specific clinical situation.18 If a patient shows nephrotoxic effects as a result of aminoglycoside therapy, the drug should be discontinued if clinically feasible, as the toxicity is usually reversible upon discontinuation of the drug. However, ototoxicity is irreversible.

Because aminoglycosides have a narrow therapeutic index, peak and trough serum levels have traditionally been measured to assess efficacy and toxicity when using a standard 3-times daily dosing regimen. Aminoglycosides work in a concentration-dependent manner, indicating that their effectiveness is measured by the peak concentration reached, which allows for “pulse dosing,” sometimes known as “once-daily dosing,” in which a high dose of the drug is given once a day. This type of regimen has been proven to be at least as efficacious as the traditional regimen and less nephrotoxic.5 However, this type of regimen is inappropriate for patients with preexisting renal dysfunction. Peaks are generally not monitored in once-daily dosing regimens, as a large enough dose is given initially to ensure that appropriate peak concentrations are reached. However, when using this type of dosing, clinicians should measure trough serum levels before administering the second dose to ensure that the drug is being eliminated from the body. The goal trough serum level is less than 0.5 mg/L. Note that these are only general recommendations for the monitoring of serum concentrations when using once-daily aminoglycoside dosing in children. Although this dosing has been studied extensively in adult patients, pediatric studies are lacking. Some institutions may attempt to extrapolate adult data to pediatric patients and measure peak or random serum concentrations when once-daily dosing is used.

If using a traditional dosing regimen, clinicians should ensure that trough concentrations are less than 2 mg/L. Peak concentrations, which are obtained 30 minutes after conclusion of a 30-minute aminoglycoside infusion, may range anywhere between 5 and 12 mg/L. However, most clinicians recommend a peak of 7 to 8 mg/L for the treatment of sepsis. When using a traditional dosing regimen, clinicians should obtain concentrations at the third dose or later to ensure that aminoglycoside levels have reached a steady state in the body. Measuring aminoglycoside levels is not generally necessary if traditional aminoglycoside therapy is likely to continue for less than 72 hours.5,18

Fluoroquinolones

The fluoroquinolones are among the most broad-spectrum antimicrobial agents currently available. The main fluoroquinolones currently used in clinical practice are ciprofloxacin, levofloxacin, and moxifloxacin.19 Moxifloxacin has limited information for use in pediatric patients and, therefore, is not discussed in this article. The fluoroquinolones work by inhibiting DNA-gyrase and topoisomerase, which causes breakage of double-stranded DNA and subsequently results in cell death in a concentration-dependent manner. Both ciprofloxacin and levofloxacin are active against a wide range of gram-negative organisms. However, ciprofloxacin is considered the fluoroquinolone of choice for the treatment of Pseudomonas infections. Levofloxacin can
cover *Pseudomonas* but should generally be reserved for use when the infecting organism has shown proven susceptibility.\textsuperscript{18}

Ciprofloxacin does not have adequate activity against most clinically important gram-positive pathogens and obligate anaerobes. Levofloxacin has broader coverage against gram-positive organisms, particularly *Streptococcus pneumoniae*, and obligate anaerobes. Some clinicians mistakenly believe that levofloxacin penetrates lung tissue to a better extent than ciprofloxacin, because it is often referred to as a “respiratory fluoroquinolone.” This belief, however, is not accurate. The term *respiratory fluoroquinolone* is merely a reference to levofloxacin’s greater coverage against *Streptococcus pneumoniae*, which is a common cause of respiratory tract infections.\textsuperscript{7,18,19}

Traditionally, fluoroquinolones have not been used as first-line therapy in pediatric patients because of the possibility of joint toxicities, specifically tendonitis and tendon rupture. Retrospective studies in pediatric patients have shown that the fluoroquinolones are generally safe to use.\textsuperscript{20,21} Nevertheless, the Food and Drug Administration issued a black-box warning for this adverse reaction in all patients, not just pediatric patients. In some cases, the empiric use of fluoroquinolones is warranted in pediatric patients, for instance when patients have allergies to other medications, such as the β-lactams, or when treating an infection that is resistant to other antimicrobials. Empiric use of fluoroquinolones in pediatric patients should generally be confined to these indications. However, clinicians should not withhold the use of the fluoroquinolones during appropriate circumstances because of fear of joint toxicity.

**Vancomycin**

Vancomycin is a glycopeptide antibiotic that inhibits bacterial cell wall synthesis via a different mechanism than the β-lactam antibiotics. It is active only against gram-positive bacteria and exerts its effects in a time-dependent manner. It is also bactericidal against all susceptible species except *Enterococcus*, for which it is only bacteriostatic. Vancomycin has long been considered the drug of choice in the treatment of resistant gram-positive infections, such as MRSA.\textsuperscript{18} Because gram-positive organisms are a common cause of sepsis, vancomycin is frequently used for treatment.

Like the aminoglycosides, vancomycin is capable of causing both nephrotoxicity and ototoxicity. However, the incidence is much lower when compared with the aminoglycosides. When vancomycin was first introduced to the market during the 1950s, the formulation contained several impurities, causing the formulation itself to become discolored, leading it to be nicknamed “Mississippi Mud.” The vast majority of reports of nephrotoxicity were associated with this impure formulation. After the formulation became more purified, reports of nephrotoxicity decreased dramatically. Although the incidence of nephrotoxicity is not as common as it once was, all patients receiving vancomycin therapy should have baseline renal function assessed with periodic monitoring thereafter.

Vancomycin also has a narrow therapeutic index. In the past, both peak and trough concentration levels were measured. However, several studies have established that peak levels do not correlate well to either efficacy or toxicity. Thus, many institutions no longer monitor peak concentrations. If a peak level is to be obtained, it should be drawn 1 hour after the conclusion of a 1-hour infusion, with a goal concentration generally between 30 and 40 mg/L. Trough concentrations should be obtained on all patients if vancomycin therapy is expected to continue for more than 72 hours. Measurement of trough concentrations should be obtained just prior to the fourth or fifth dose to ensure that a steady state has been reached. For sepsis, the recommendation is that trough concentrations be between 15 and 20 mg/L.\textsuperscript{18,22}

**Cardiovascular Agents**

Upon stabilization of airway and breathing, appropriate optimization and support of end organ perfusion must occur. Improving blood pressure and cardiac output is necessary in patients with sepsis and can be achieved through the optimization of preload, SVR, and the increase of cardiac contractility. Cardiac output is the product of heart rate and stroke volume; in turn, stroke volume depends on preload, myocardial contractility, and afterload. Mean arterial pressure (MAP) is derived from the product of SVR and cardiac output.\textsuperscript{23,24}

Agents used in the management of sepsis include vasopressors and inotropes. Vasopressor and inotropic agents function either through the stimulation of adrenergic receptors or through the induction of intracellular processes increasing cyclic adenosine monophosphate.
Vasopressors improve perfusion, preserve cardiac output through an increase in MAP, improve cardiac preload, and increase cardiac output by decreasing venous compliance and augmenting venous return. In addition, they cause arteriole vasoconstriction, thus increasing blood pressure. Inotropic agents improve oxygen delivery and cardiac output through an increase in rate and contractility. Potential agents used in the treatment of sepsis include, but are not limited to, epinephrine, norepinephrine, vasopressin, dopamine, dobutamine, and milrinone (see Table 4). Pediatric patients are at an increased risk of medication errors, especially with continuous infusions used in critical areas. Therefore, precaution should be observed in the dosing, distribution, and administration of these medications. Determination of timing, type, and quantity of vasopressor or inotropic support should be adjusted and titrated on the basis of the individual need of the patient.

Dopamine increases cardiac output by improving myocardial contractility and decreasing heart rate. It is a precursor to norepinephrine and epinephrine. Dopamine works by releasing norepinephrine from sympathetic vesicles as well as acting directly on α-adrenergic receptors. Dopamine’s systemic effects are dose dependent. At doses less than 5 mcg/kg per minute, dopamine receptors are activated with renal and mesenteric vasodilation. Increasing the dose to 5 to 10 mcg/kg per minute results in β₁-adrenergic receptor stimulation and increases inotropic and chronotropic effects. Doses greater than 10 mcg/kg per minute stimulate α₁-adrenergic effects, leading to arterial vasoconstriction. On the basis of results from the Australian and New Zealand Intensive Care Society clinical trial, a study examining low-dose dopamine in patients with early renal dysfunction, low-dose or “renal dose” dopamine is no longer recommended. The trial showed no clinical benefit in decreasing the incidence of renal failure or ruling out the need for renal replacement therapy. Dopamine is associated with tachycardia and arrhythmias, and therefore patients should be monitored closely for the development of these adverse effects.

Dobutamine is an inotropic agent that has mixed effects on β₁- and β₂-adrenergic receptors, increasing heart rate and cardiac contractility. Clinical effects observed include redirecting blood flow away from the skeletal muscle to the splanchnic circulation, elevating SVR, elevating diastolic blood pressure, and decreasing pulse pressures. Dobutamine may be useful in pediatric patients with low cardiac output states. An increase in serum potassium level has been noted with the use of dobutamine. Therefore, potassium levels should be monitored closely.

Epinephrine is a circulating catecholamine hormone that is synthesized from norepinephrine. It has both α- and β-adrenergic properties. Exogenously administered epinephrine increases heart rate (chronotrope) and stroke volume (inotrope), which increases cardiac output and cardiac oxygen consumption.

### Table 4: Vasopressors Used in the Treatment of Sepsis

<table>
<thead>
<tr>
<th>Cardiovascular Agent</th>
<th>Clinical Effects</th>
<th>Dose (Titrate to Achieve Desired Clinical Response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine</td>
<td>Increased HR, increased cardiac contractility, increased SVR, increased BP, and decreased pulse pressure</td>
<td>2-20 mcg/kg per minute</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Increased cardiac output, increased inotropic effects, and increased HR and arterial vasoconstriction</td>
<td>2 mcg/kg per minute titrated upward to 10 mcg/kg per minute</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Increased HR, decreased SV, and increased cardiac output</td>
<td>0.02 mcg/kg per minute titrated upward to 1 mcg/kg per minute</td>
</tr>
<tr>
<td>Milrinone</td>
<td>Increased myocardial contractility, increased venous and arterial dilation, and decreased preload and SVR</td>
<td>50 to 75 mcg/kg per minute load over 20 min, followed by a continuous infusion of 0.5 to 1 mcg/kg per minute</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Increased MAP and vasoconstriction</td>
<td>0.05-1 mcg/kg/min</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>Increased SVR and vasoconstriction</td>
<td>0.03-2 miliUnits/kg per minute</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; HR, heart rate; MAP, mean arterial pressure; SV, stroke volume; SVR, systemic vascular resistance.
Doses of epinephrine range from 0.02 mcg/kg per minute titrated upward to 1 mcg/kg per minute to achieve the desired clinical response. According to Irazuzta et al., epinephrine may be a reasonable option for the treatment of patients with low cardiac output and poor peripheral perfusion. Epinephrine has been shown to stimulate gluconeogenesis and glycolysis, as well as inhibit the action of insulin, leading to increased blood glucose concentrations. Infusions of epinephrine have been observed to increase serum lactate levels as a result of epinephrine's ability to cause skeletal muscles to release lactic acid, which is then transported to the liver for glucose synthesis. This effect can result in decreased splanchnic blood flow and increased regional lactic acidosis; therefore, monitoring of lactate is recommended. Negative effects associated with the use of epinephrine include a decrease in gastric blood flow and tachyarrhythmias.

Norepinephrine is a potent α-adrenergic agonist, with less effect on β-adrenergic receptors. It increases MAP as a result of vasoconstriction, with little change in heart rate and less increase in stroke volume compared with dopamine. Norepinephrine may also be more effective for fluid-refractory hypotensive patients with septic shock.

Vasopressin is a peptide hormone synthesized in the hypothalamus that regulates retention of water by the body. It is released in response to decreased blood volume and osmolarity. The American College of Critical Care Medicine guidelines recommend the use of vasopressin in patients with refractory septic shock, despite adequate fluid resuscitation and conventional vasopressors. Vasopressin is rapidly metabolized by the liver and kidney, with a half-life of 10 to 30 minutes. Because of the potent vasoconstriction of vasopressin, patients should be monitored for coronary, mesenteric, and cutaneous ischemia if high doses are administered. Urinary and cardiac output should be monitored if vasopressin is initiated.

Milrinone, a phosphodiesterase inhibitor used in the management of sepsis, works by breaking down cyclic adenosine monophosphate, which increases myocardial contractility and venous and arterial dilation, thereby decreasing preload and SVR. Milrinone also aids in afterload reduction and myocardial diastolic relaxation (lusotropic effect). Milrinone has a long elimination half-life, which may limit its use. Milrinone is associated with tachyarrhythmias and must be dose adjusted for renal impairment.

Steroid Use
The role of corticosteroids in sepsis and septic shock is an ever-evolving topic. Corticosteroids work in sepsis to suppress the production of cytokines and increase the sensitivity of the cardiovascular system to endogenous or exogenous catecholamines, which improves myocardial contractility, stroke volume, effective circulating blood volume, systemic vascular resistance, and urine output. Patients with sepsis have also been shown to experience adrenal insufficiency, which can be corrected through the use of steroids, particularly hydrocortisone.

The research surrounding the use of steroids in adults with septic shock is abundant; however, their exact effect on mortality rate is still controversial. Several early adult studies have shown that the use of high-dose steroids decreases time to the resolution of septic shock but failed to show a decrease in mortality rate. Other studies using physiological doses of steroids showed a reduction in the time needed for shock reversal and a reduction in the time to the cessation of vasopressor use. An additional larger multicenter, randomized, controlled trial undertaken in patients with vasopressor-unresponsive septic shock was able to demonstrate a reduction in mortality rate in all steroid-treated patients. Furthermore, a decrease in the time to shock resolution was shown in patients who had been found to have a relative adrenal insufficiency, defined as having a suboptimal adrenocorticotropic hormone cortisol response.

Randomized controlled trials in pediatric patients are unsurprisingly sparse. For this reason, in contrast to adult patients, the recommendation of the Surviving Sepsis Campaign for pediatric patients specifies that therapy with hydrocortisone be reserved for children with catecholamine resistance and suspected or proven adrenal insufficiency. Pediatric patients at high risk for adrenal insufficiency include those children with purpura fulminans, children who have previously received steroid therapy for a chronic illness, and children with pituitary or adrenal abnormalities. In the case of catecholamine-resistant septic shock, absolute adrenal insufficiency (most commonly seen in children) can be defined as a random total cortisol level of less than 18 mcg/dL. Relative adrenal insufficiency has been defined as an increase in cortisol of 9 mcg/dL or more, measured by an
adrenocorticotropic hormone stimulation test 30 to 60 minutes after administration of cosyntropin.\textsuperscript{10,13,26}

For pediatric patients meeting the minimum criteria for the use of steroids, the Surviving Sepsis Campaign recommends the use of hydrocortisone at a dose of 50 mg/m\textsuperscript{2} per day (ie, stress dose). Other literature recommends using hydrocortisone at a dose of 2 to 30 mg/kg per day, divided every 6 hours, or 1 to 2 mg/kg per hour as a continuous infusion.\textsuperscript{26} Doses as high as 50 mg/kg per day of hydrocortisone have been used in septic shock.\textsuperscript{2} Hydrocortisone is recommended over dexamethasone because of the possibility of dexamethasone causing immediate and prolonged suppression of the hypothalamic-pituitary-adrenal axis.\textsuperscript{10,13} Hydrocortisone therapy may be weaned after vasopressors are discontinued; some studies recommend a minimum of 5 to 7 days of steroids.\textsuperscript{10,13,26}

Glucose Control in Sepsis

Monitoring and maintenance of appropriate glucose levels in pediatric patients with sepsis are of utmost importance. Hyperglycemia occurs commonly in sepsis and is thought to be caused by peripheral resistance to insulin and increased gluconeogenesis,\textsuperscript{26} which can be further compounded by the administration of excess dextrose in IV fluids and total parenteral nutrition. Hyperglycemia can produce endothelial dysfunction by impairing the phagocytic function of neutrophils and macrophages.\textsuperscript{10} Higher rates of mortality have been demonstrated in critically ill patients with hyperglycemia. The increase in mortality rate is independently associated with glucose level, with one pediatric study associating higher mortality rates with glucose levels greater than 178 mg/dL.\textsuperscript{26,31} Another study showed that glucose measurements greater than 150 mg/dL were associated with a higher mortality rate.\textsuperscript{31} The length of the hyperglycemic state is also proportionately related to the increase in mortality rate.\textsuperscript{26}

The appropriate treatment of hyperglycemia associated with sepsis is controversial. Adult studies have shown conflicting results for the need for tight glycemic control and insulin therapy. An early adult study showed that the use of intensive insulin therapy, defined as a blood glucose concentration maintained between 80 and 110 mg/dL, decreased all-cause mortality in patients being treated with mechanical ventilation from 8\% to 4.6\%.\textsuperscript{10,32} Subsequent studies, particularly the Volume Substitution and Insulin Therapy in Severe Sepsis trial, have shown that intensive insulin therapy is associated with an increase in hypoglycemia, higher rates of serious adverse events, and no difference in mortality versus conventional management of hyperglycemia.\textsuperscript{10} Studies evaluating strict insulin therapy in pediatric patients are scarce.\textsuperscript{13,31} Current recommendations for adult patients from the Surviving Sepsis Campaign are to use insulin therapy to maintain a blood glucose level lower than 150 mg/dL, with frequent glucose monitoring. These same guidelines state that it is reasonable to use insulin therapy to prevent prolonged periods of hyperglycemia in pediatric patients with sepsis.\textsuperscript{13} The need for insulin typically decreases approximately 18 hours after the onset of shock.\textsuperscript{2}

Hypoglycemia also can occur in pediatric patients with sepsis. It is most commonly seen in infants and can cause neurological sequelae if not promptly diagnosed and treated. It can be

<table>
<thead>
<tr>
<th>Table 5: Information Resources Available to Health Care Professionals, Patients, and Families About Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>The National Institute of General Medical Sciences (<a href="http://www.nigms.nih.gov">http://www.nigms.nih.gov</a>) provides health care professionals and the public with information related to disease diagnosis, treatment, and prevention. This Web site is part of the National Institutes of Health and the US Department of Health and Human Services.</td>
</tr>
<tr>
<td>Medline Plus (<a href="http://www.nlm.nih.gov/medlineplus/sepsis.html">http://www.nlm.nih.gov/medlineplus/sepsis.html</a>) provides general information on pediatric sepsis as well as links to patient handouts in English and Spanish. It is funded by the US National Library and the National Institutes of Health.</td>
</tr>
<tr>
<td>The Journal of the American Medical Association (<a href="http://jama.jamanetwork.com/article.aspx?volume">http://jama.jamanetwork.com/article.aspx?volume</a> = 304&amp;issue = 16&amp;page = 1856) provides access to a free article that can be photocopied noncommercially by physicians and other health care professionals to share with patients.</td>
</tr>
<tr>
<td>Surviving Sepsis Campaign (<a href="http://www.survivingsepsis.org">http://www.survivingsepsis.org</a>) provides information about the campaign for health care professionals. Patients and families can access information on the signs and symptoms of sepsis, and it provides a link to videos that can be viewed.</td>
</tr>
</tbody>
</table>

Copyright © 2012 American Association of Critical-Care Nurses. Unauthorized reproduction of this article is prohibited.
prevented by administering glucose at rates ranging between 2 and 8 mg/kg per minute, depending on the age of the child.\textsuperscript{2,13} Dextrose 10\% with sodium chloride solution is recommended by the Surviving Sepsis Campaign guidelines.\textsuperscript{13}

**Conclusion**

Sepsis is a serious inflammatory condition caused by an overwhelming infection, which, in turn, could be caused by a multitude of different microorganisms and can lead to several severe adverse consequences. Prompt assessment and treatment with fluids, antibiotics, and, when needed, vasopressor or inotrope therapy should occur. Additional therapies such as hydrocortisone or insulin may be needed in some patients who have catecholamine resistance or hyperglycemia. Further research is needed in pediatric patients to elucidate the optimal use of these and other therapies. For more information about sepsis, please note the resources listed in Table 5.

**REFERENCES**


