Empiric Antibiotics for the Complex Febrile Child: When, Why, and What to Use

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There are multiple patient care scenarios where empiric antibiotics are indicated in the practice of pediatric emergency medicine. Patients with fever and neutropenia, ventriculoperitoneal shunt(s), cystic fibrosis, and short bowel syndrome are unique patient populations that are often instructed to seek further evaluation for any concerns of possible infection. When seen in the emergency department, fever is usually the presenting complaint; however, they may also present with more subtle signs and symptoms of infection that require prompt evaluation. This article briefly reviews these 4 unique patient populations as well as when, why, and what empiric antibiotics are often used to treat them.

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Although the cause of fever in the otherwise healthy child is usually of benign etiology, fever in a child with a chronic medical condition or indwelling hardware (ventriculoperitoneal [VP] shunt, central venous catheter) is often a sign of a serious underlying infection. Because of repeated infections, these children tend to develop more complicated infections, often with drug-resistant organisms. It is important for the emergency department (ED) physician to understand not only the likely etiologies of these infections but which antibiotic therapies are appropriate for empiric treatment on presentation.

Empiric Antibiotics in Patients with Fever and Neutropenia

Neutropenia can be congenital, idiopathic, and/or acquired in etiology. The causes of acquired neutropenia include infections, immune disorders, nutritional deficiencies, chemicals, and medications. Patients with fever and neutropenia are at risk for serious infection. Empiric antibiotics included in this section are based on guidelines for patients with cancer receiving chemotherapy but are applicable to most patients with fever and neutropenia regardless of etiology.

Patients with cancer are at greater risk of infection if they have central venous catheters and when their absolute neutrophil count (ANC) decreases during chemotherapy. The ANC is calculated by multiplying the total white blood cell (WBC) count by the combined percentage of segmented neutrophils and bands (ANC = WBC count × percentage [neutrophils + bands]). It is thought that at least one half of neutropenic patients who become febrile have an established or occult infection and at least one fifth of febrile patients with neutrophil counts of less than 100 cells per cubic millimeter have bacteremia [1].

The Infectious Diseases Society of America issued guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever in 1990 that were revised in 1997 [2]. The Infectious Diseases Society of America Fever and Neutropenia Guidelines Panel issued guidelines in 2002 for the use of antimicrobial agents in neutropenic patients with cancer. Neutropenia is defined as an ANC less than 500 cells per cubic millimeter or less than 1000 cells per cubic millimeter. Fever has been defined as a single oral temperature of at least 38.3°C.
Empiric Antibiotics for Patients with VP Shunt(s)

Cerebrospinal fluid (CSF) shunt placement is the most common pediatric neurosurgical procedure performed. As a result of very high complication rates, patients with VP...
shunts are frequently brought to the ED for evaluation of suspected malfunction. Although obstruction is the most common complication, infection is responsible for 20% to 25% of all shunt complaints [6]. Seizures, ventriculitis, meningitis, and subdural empyema are secondary problems that can develop as a result of shunt infections.

Half of all VP shunt infections are observed during the initial 2 weeks after placement, and 75% occur within the first 2 months. Among patients beyond 6 months from surgery, shunt infection is very unlikely [7].

Most shunt infections occur because of colonization of the shunt at the time of surgery or, less frequently, secondary to skin breakdown of the postoperative wound. These proximal shunt infections are predominantly caused by low-virulence organisms found in skin flora. The typical presentation involves nonspecific complaints of fever without a source, poor feeding, or not acting right. The classic symptoms of shunt infection such as headache, lethargy, fever, and meningismus are less likely. Meningismus is present in only 25% of cases, with headache occurring in 5% to 10% and lethargy in 10% to 15% of patients with shunt infections [8,9]. Fever is present in 80% to 90% of cases, but the absence of fever does not exclude the possibility of infection [10]. In reality, clinical signs of increased intracranial pressure may develop only when infection has caused shunt obstruction and subsequent malfunction.

The most commonly cultured organisms are Staphylococcus epidermidis (40–50%), S aureus (25%), and Propionibacterium acnes [11]. Patients with VP shunts also have an increased risk of meningitis caused by the traditional pathogens S pneumoniae, Neisseria meningitidis, and Haemophilus influenzae. Reports of fungal central nervous system infections have increased in recent years especially because of Candida species.

Ventriculoperitoneal shunt infections may also develop via direct contamination of the distal end of the shunt by hematogenous seeding. These infections manifest as abdominal pain due to bowel perforation and peritonitis or pseudocyst formation with distal obstruction. In addition to Staphylococcus species, gram-negative organisms or mixed flora may be isolated. Patients with gram-negative VP shunt infections are usually more ill appearing. Particularly at risk for gram-negative shunt infections are infants younger than 6 months. The rate of infection is twice that of children at least 1 year of age at the time of the shunt insertion [10].

In patients with VP shunts, wound infections are usually located over the site of the reservoir or in the abdominal wall. Infection generally occurs at the time of shunt placement and appears as warmth, redness, and possible purulent drainage at the affected surgical site. Staphylococcus species are the most frequently cultured organism.

Any patient presenting with complaints that are suspicious for a shunt problem should be evaluated with a thorough history and physical examination. If the possibility of infection remains, a diagnostic evaluation should be initiated; and prompt neurosurgical consultation should be obtained. Laboratory tests are of limited value in determining the probability of VP shunt infection. It has been demonstrated that even with a documented shunt infection, 25% of patients will have a normal WBC count [12]. Analysis of CSF is necessary, and a shunt tap is preferred to lumbar puncture because it can identify obstruction and is more sensitive in detecting infection. This is important because one third of patients with shunt obstruction are found to have a concurrent shunt infection. The CSF should be sent for cell count, glucose, protein, gram stain, and culture. Cerebrospinal fluid cultures are critical for organism identification and directing further antibiotic therapy. The other component necessary when evaluating a shunt is radiographic imaging. Plain radiographs of the shunt valve and tubing are needed to assess the continuity of the system and to rule out kinking of the tube. Cranial computed tomography is used to demonstrate evidence of ventriculitis or CSF obstruction. Comparison with a previous computed tomography is essential, as children with VP shunts often do not have normal baseline ventricular size even with a normally functioning shunt [11].

Treatment of an infected shunt involves removal of the shunt, sterilization of CSF with antibiotics, and placement of a new shunt. It is essential to give the first dose of intravenous antibiotics in the ED. Empiric parenteral antibiotic coverage includes vancomycin and a third-generation cephalosporin (cefotaxime) for endogenous gram-positive and gram-negative pathogens in children. Vancomycin combined with ceftazidime, cefepime, or meropenem is indicated to cover nosocomial gram-positive and gram-negative pathogens in adults [13]. Linezolid may have utility in treating infections caused by resistant S aureus [14]. If an organism is known or sensitivities are available, more specific antibiotic coverage can be selected (Table 1).

### Table 1 Recommended parenteral therapy for known organisms in VP shunt infections.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Antibiotics</th>
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<tbody>
<tr>
<td>S epidermidis</td>
<td>Vancomycin ± rifampicil</td>
</tr>
<tr>
<td>S aureus</td>
<td>Oxacillin or nafcillin</td>
</tr>
<tr>
<td>Gram-negative</td>
<td>Cefotaxime, cefepime, or meropenem</td>
</tr>
<tr>
<td>P acnes or Streptococcus species</td>
<td>Penicillin G ± gentamicin</td>
</tr>
<tr>
<td>Fungi</td>
<td>Amphotericin B</td>
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Empiric Antibiotics in Patients with Cystic Fibrosis

Patients with cystic fibrosis (CF) often present to the ED for evaluation and treatment of pulmonary exacerbations.
It is extremely important to diagnose and treat new or worsening infections to limit progression of chronic lung disease. Furthermore, a variety of factors make the eradication of respiratory pathogens in children with CF especially difficult (Table 2).

In early disease, infections are associated with acute respiratory complaints and new physical findings. Over time, a repeating cycle of infection, inflammation, and structural injury leads to end-stage lung disease and bronchiectasis. Once chronic lung disease has developed, acute exacerbations can be difficult to diagnose. The following clinical features have been found to concur with the criterion standard of physician diagnosis of a pulmonary exacerbation in CF: increased cough, increased sputum production or chest congestion, increased fatigue, decreased appetite, increased respiratory rate or dyspnea at rest, change in sputum appearance, fever, increased nasal congestion or drainage, and decreased exercise tolerance or increased dyspnea with exertion [15].

Treatment of any pulmonary exacerbation in patients with CF is highly individualized. Antibiotic selection is dictated by the severity of the exacerbation, the extent of existing underlying lung disease, and the patient’s respiratory tract flora. Mild to moderate exacerbations can be successfully treated with oral antibiotics. Intravenous antibiotics are indicated for severe exacerbations, treatment failure associated with previously administered oral antibiotics, or infections caused by resistant organisms. Antibiotics should be directed against any new pathogen detected in the respiratory secretions. If no such organism is identified, the most recent respiratory culture and sensitivity results for each patient should guide the initial antibiotic choice.

*Staphylococcus aureus* is the most common pathogen isolated in infants and young children with pulmonary exacerbations. *Haemophilus influenzae* and *Pseudomonas aeruginosa* are more prevalent in older children and adults. Mild exacerbations due to *S. aureus* and *H. influenzae* may be effectively treated with trimethoprim-sulfamethoxazole, amoxicillin-clavulanic acid, or oral cephalosporins. Intravenous cephalosporins are recommended for more serious *S. aureus* and *H. influenzae* infections. The emergence of antimicrobial resistance has greatly impacted on the treatment of patients with CF. The prevalence of MRSA among patients with CF reported to the CF Foundation Patient Registry increased from 7% in 2001 to 19% in 2006 [16]. A combination of nebulized vancomycin, oral rifampin, and sodium fusidate has been used to effectively treat less serious MRSA infections. A tetracycline (doxycycline) and linezolid are other oral choices for mild to moderate MRSA exacerbations. Vancomycin or teicoplanin is recommended for severe infections requiring intravenous therapy.

Isolation of *P. aeruginosa* in the sputum represents an important transition in the pulmonary status of patients with CF. Pseudomonal infection leads to a more rapid decline in lung function and an increase in mortality. The initial isolation and presumed infection may respond well to oral fluoroquinolones used in combination with aerosolized tobramycin. Patients with chronic infection, however, may be colonized with several strains of *Pseudomonas* species in their sputum; and identifying the strain responsible for acute infection can be a challenge. The most commonly chosen intravenous regimens for *P. aeruginosa* infections combine aerosolized tobramycin treatments with a semisynthetic penicillin (ticarcillin-clavulanic acid or piperacillin-tazobactam), a third-generation cephalosporin (cefazidime), a fourth-generation cephalosporin (cefpime), or a carbapenem (imipenem-cilastatin or meropenem). A recent comparative trial of intravenous tobramycin and meropenem or ceftazidime found the 2 options to be equally effective in the treatment of CF patients with pseudomonal lung infections [17]. Regardless of the combination chosen, guidelines recommend the addition of vancomycin or linezolid for those patients found to be coinfect with *P. aeruginosa* and MRSA.

When patients fail to respond to conventional therapy, other diagnoses should be considered. *Burkholderia cepacia* is a plant pathogen that can cause severe pulmonary disease in patients with CF. Both cefazidime and meropenem have shown activity against some strains of *B. cepacia*. Tobramycin should be added for resistant strains. Allergic bronchopulmonary aspergillosis is a reaction to a type of fungus that can occur in association with CF. The fungus does not invade and destroy the lung tissue, but instead colonizes the airways and causes recurrent inflammation. Recommended treatment consists of oral prednisone and itraconazole. Finally, infection with atypical mycobacteria is not common, but can occur in young children with CF. Treatment is generally prolonged and requires the selection of a multiple drug combination based on the specific organism involved.

### Table 2  Factors that contribute to the difficulty in eradicating respiratory pathogens in children with CF.

<table>
<thead>
<tr>
<th>Development of antibiotic resistance</th>
<th>Poor penetration of antibiotics through respiratory secretions</th>
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<tr>
<td>Defects in host mucosal defenses</td>
<td>Very slow growing bacteria often involved</td>
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<tr>
<td>Bacterial produced “biofilms” that interfere with phagocytic killing</td>
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### Empiric Antibiotics in Patients with Short Bowel Syndrome

Short bowel syndrome can result from congenital or acquired reasons. Congenital etiologies include gastrointestinal, intestinal atresia, and midgut volvulus; and acquired etiologies include necrotizing enterocolitis or Crohn’s disease. Long-term parenteral nutrition has resulted in improved long-term survival and quality of...
life in this patient population; for that reason, patients with short bowel syndrome require prolonged use of central venous catheters. Consequently, parenteral nutrition–associated liver failure and catheter-related bacteremia are the leading causes of morbidity and mortality in patients with short bowel syndrome [18,19].

Initial evaluation of patients with short bowel syndrome should include a physical examination, comprehensive metabolic panel, complete blood cell count, and blood cultures from a peripheral vein and/or all central line lumens. Additional laboratory and radiological testing should be performed as indicated by the history and physical examination. Consultation with local gastroenterology and infectious disease specialists is recommended.

Patients with short bowel syndrome are at increased risk of infection from both endogenous and nosocomial pathogens. Gram-negative bacteria, specifically E coli, Enterobacter species, Klebsiella species, Proteus species, and Pseudomonas species, are prominent causes of infection. Infection with gram-negative bacteria may be secondary to external contamination or bacterial translocation. Gram-positive organisms, specifically, S epidermidis and S aureus, and Candida species are also associated with external contamination [20,21].

Empiric broad-spectrum parenteral antibiotics are initiated to cover gram-negative and gram-positive bacteria. Antibiotic therapy choices include a third-generation cephalosporin (cefotaxime or ceftazidime), a carbapenem (imipenem-cilastatin or meropenem), or a semisynthetic penicillin (ticarcillin–clavulanic acid or piperacillin-tazobactam). Vancomycin is added for coverage of gram-positive bacteria including MRSA. An aminoglycoside (gentamicin, tobramycin, or amikacin) may be used for gram-negative bacteria including E coli, Enterobacter species, Klebsiella species, Proteus species, and Pseudomonas species. Aminoglycosides may be used for gram-negative coverage in patients with no renal insufficiency.

The choice of antibiotic therapy should be guided by the patient's previous culture results and sensitivities as well as local antibiotic resistance patterns whenever possible. Lastly, if fungal infection is suspected, empiric antifungal therapy should also be initiated with an amphotericin formulation.

**Relevant Antibiotic Alerts**
The US Food and Drug Administration (FDA) initiated a safety review of cefepime in November 2007 after concerns of increased mortality in patients treated with cefepime were raised in a published meta-analysis. In May 2008, the FDA announced it was continuing to review safety data concerning cefepime [22,23]. Additionally, the FDA initiated a safety review of linezolid in March 2007 after concerns of increased mortality in patients with catheter-related bacteremia and catheter site infections treated with linezolid were raised in an open-label randomized trial. The chance of death was related to the type of organism causing infection, with no difference in mortality in patients with gram-positive infections and higher mortality in patients with gram-negative—only, mixed, or no organism infections. Linezolid is not approved for the treatment of catheter-related bloodstream, catheter site, or gram-negative infections [24].

**Summary**
Children with fever and neutropenia, VP shunt(s), CF, and short bowel syndrome frequently present in the ED with a complaint of fever with or without additional signs and symptoms. In addition to a thorough evaluation and stabilization of the patient, the ED physician is often responsible for initiating empiric antibiotics to treat suspected bacterial infections in these complex febrile children. The choice of a particular empiric antibiotic regimen may vary depending on the individual patient and suspected infection as well as local antimicrobial susceptibility patterns. This article summarizes several available antibiotic treatments. Consultation with subspecialty services, if available, is recommended.

**References**