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Children's Hospital Association
Improving Pediatric Sepsis Outcomes Collaborative

Empiric Antimicrobial Treatment Recommendations for Pediatric Severe Sepsis

From the Improving Pediatric Sepsis Outcomes Collaborative Infectious Disease/Infection Prevention Work Group, whose members are experts in antimicrobial treatment from 15 children's hospitals.

2018 Version

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These *Recommendations* for empiric antimicrobial treatment of pediatric severe sepsis were developed as part of the comprehensive IPSO resuscitation bundle for use by children's hospitals participating in the Improving Pediatric Sepsis Outcomes Collaborative.

These *IPSO Recommendations* are included in the Massachusetts Sepsis Consortium's Emergency Department tool kit by special permission from Children's Hospital Association for use as part of a bundle of care for children with severe sepsis and prior to transfer to a tertiary care children's hospital.

Recommendations for Empiric Antimicrobial Treatment of Severe Sepsis with No Suspected/Identified Site of Infection

- ✓ With each treatment regimen, administer the first agent listed within 1 hour, followed by the additional agents.
- ✓ If the patient has an allergy or serious intolerance of the recommended agents, consult pediatric infectious diseases.
- ✓ **Abbreviations**: CNS, central nervous system; CL, central line; LP, lumbar puncture with analysis of cerebrospinal fluid; MDR-GNB, multidrug resistant-Gram negative bacillus

Patient age **< 4 weeks**

Does not apply to infants cared for in a neonatal ICU.

ampicillin[a] + 3rd/4th generation cephalosporin[b,c] + acyclovir

a. if CL or other invasive device present at onset or if suspect S. aureus infection, replace with vancomycin
b. cefotaxime, ceftazidime, cefepime per institutional reference
c. if CNS infection excluded, consider replacing with gentamicin

Patient age **> 4 to 8 or 12 weeks**

Does not apply to infants cared for in a neonatal ICU.
Institutional preference for 8 vs. 12 weeks.

ampicillin[a] + ceftriaxone[b,c]

a. if CL or other invasive device present at onset or if suspect S. aureus infection, replace with vancomycin
b. if CNS infection excluded, consider replacing with gentamicin
c. if suspect staphylococcal or streptococcal toxic shock syndrome, add clindamycin

Patient age **> 8 or 12 weeks**

Does not apply to infants cared for in a neonatal ICU.
Institutional preference for 8 vs. 12 weeks.

ceftriaxone + vancomycin[a]

a. if suspect staphylococcal or streptococcal toxic shock syndrome, add clindamycin

- if suspect bowel or other anaerobic source, replace cephalosporin and ampicillin with piperacillin/tazobactam[1] or add metronidazole
- if immunocompromised or suspect *Pseudomonas* infection[2], replace cephalosporin with ceftazidime, cefepime, piperacillin/tazobactam[1] or meropenem[3]
- if suspect MDR-GNB infection[4], replace cephalosporin or piperacillin/tazobactam with meropenem and consider adding gentamicin, tobramycin or a quinolone

if immunocompromised or other risk factor present (intestinal failure, burn), consider adding fluconazole, caspofungin or micafungin

[1] Use of vancomycin and piperacillin/tazobactam in combination should be avoided whenever possible, especially in children who have or are at high-risk for renal insufficiency. Use of this combination should be reassessed daily and, preferably, revised or discontinued within 2 days.
[2] History of previous *Pseudomonas* colonization, history of recent broad-spectrum antibiotic use during the previous 14 days, presence of tracheostomy or central line, or hospitalization for >72 hours during the past 90 days inclusive of the current hospitalization.
[3] Do not use meropenem routinely or in preference over other anti-*Pseudomonas* agents unless justified by local antibiogram or history of colonization with ceftazidime/cefepime/piperacillin/tazobactam-resistant *Pseudomonas* or other MDR-GNB. Consult pediatric infectious diseases
[4] Currently receiving broad-spectrum Gram-negative therapy, such as cefepime, ceftazidime, piperacillin/tazobactam, ciprofloxacin or levofloxacin, or history of exposure to a setting with a high prevalence of colonization with MDR-GNB, such as long-term care, adult-care hospitals, or country of origin. Consult pediatric infectious diseases.

Recommendations for Empiric Antimicrobial Treatment by Site of Suspected/Identified Infection

The recommendations in the following tables are for patients with severe sepsis when a specific site of infection has been identified, such as severe skin/soft tissue infection/necrotizing fasciitis.
These recommendations may also be used for patients who have a specific site of infection identified and do not have severe sepsis OR who have been treated for severe sepsis and have responded to treatment adequately.

Condition	Recommendation	Rationale	Examples of antibiotics that could be used
Community-acquired pneumonia, uncomplicated	Empiric treatment regimens should provide coverage for encapsulated bacteria	Common pathogens for can be treated with narrow coverage	Ampicillin
Community-acquired pneumonia, complicated (eg, necrotizing pneumonia, empyema)	Empiric treatment regimens with coverage for encapsulated bacteria and *Staph. aureus* including MRSA	Complicated pneumonia may be caused by *Staph. aureus* including MRSA	Ceftriaxone and vancomycin (or other antibiotic which provides reliable MRSA coverage based on local antibiogram e.g. clindamycin)
Aspiration pneumonia, uncomplicated	Empiric treatment regimens with coverage for normal oral flora	Aspiration pneumonia may be caused by common oral flora	Ampicillin, ampicillin/sulbactam or ceftriaxone
Aspiration pneumonia, complicated	Empiric treatment regimens with aerobic Gram negative, including *Pseudomonas*, and anaerobic coverage	Aspiration pneumonia may be caused by aerobic Gram negative, including *Pseudomonas*, and anaerobic bacteria	Piperacillin/tazobactam, cefepime and metronidazole, or meropenem (if colonized with MDR-GNR*)
Ventilator associated pneumonia	Empiric treatment regimens with encapsulated organisms, *Staph. aureus* and aerobic Gram negative coverage, including *Pseudomonas* aeruginosa	Ventilator associated pneumonia may be caused by encapsulated organisms, *Staph. aureus* and aerobic Gram negative, including *Pseudomonas* MRSA coverage if known to be colonized with MRSA	Cefepime or piperacillin/tazobactam, plus vancomycin if colonized with MRSA

Condition	Recommendation	Rationale	Examples of antibiotics that could be used
CNS infection, meningitis, encephalitis	Empiric treatment regimens with good CNS penetration	Bactericidal activity in CSF is necessary for optimal treatment	Ceftriaxone, ceftazidime or cefepime and vancomycin Acyclovir for neonates, consider for older infants and children
CNS infection, brain abscess or subdural empyema	Empiric treatment regimens with good CNS penetration and with penicillin-resistant streptococci, MRSA and anaerobe coverage	Bactericidal activity in CSF is necessary for optimal treatment Infections may be polymicrobial including penicillin-resistant streptococci, MRSA and anaerobes	Ceftriaxone, ceftazidime or cefepime and vancomycin and metronidazole
CNS infection, CSF shunt infection	Empiric treatment regimens with good CNS penetration with *Staph. aureus*, including MRSA, coagulase negative staphylococcal and aerobic Gram negative coverage	Bactericidal activity in CSF is necessary for optimal treatment CSF infection may be caused by Staph. aureus, including MRSA, coagulase negative staphylococcal and aerobic Gram negative coverage	Ceftriaxone, ceftazidime or cefepime and vancomycin
Skin/soft tissue infection, not severe	Empiric treatment regimens effective against *Staph. aureus*, including MRSA, and streptococci	Common pathogens can be treated with narrow coverage	Cefazolin and/or vancomycin (or other antibiotic which provides reliable MRSA coverage based on local antibiogram e.g. clindamycin)
Severe skin/soft tissue infection/necrotizing fasciitis	Empiric treatment regimens with coverage for Gram positive, Gram negative and anaerobic bacteria, including toxin-producing bacteria	Infections may be polymicrobial, including anaerobes Clindamycin is a protein synthesis inhibitor, which may reduce toxin production	Piperacillin/tazobactam and vancomycin or cefepime, metronidazole and vancomycin plus clindamycin

Condition	Recommendation	Rationale	Examples of antibiotics that could be used
Toxic shock syndrome (e.g., fever, rash, shock, organ dysfunction)* * see recommendations for severe skin/soft tissue infection/ necrotizing fasciitis	Empiric treatment regimens for no identified source plus coverage for MRSA, including toxin-producing bacteria	Clindamycin is a protein synthesis inhibitor, which may reduce toxin production	Ceftriaxone, ceftazidime, or cefepime and vancomycin plus clindamycin
Bone and joint infection	Empiric treatment regimens effective against *Staph. aureus*, including MRSA, *Kingella*, and streptococci	Common pathogens can be treated with narrow coverage	Cefazolin and/or vancomycin (or other antibiotic which provides reliable MRSA coverage based on local antibiogram e.g. clindamycin and *Kingella*)
Fever and neutropenia, and other severely immunocompromised patients	Empiric treatment regimens with coverage for Gram positive and Gram negative bacteria, including *Pseudomonas* Empiric treatment for penicillin-resistant streptococci, MRSA, or drug-resistant Gram negative bacilli should be added for patients who are clinically unstable, when a beta-lactam-resistant bacteria is suspected, or for centers or patient populations with a high rate of resistant pathogens Empiric treatment for anaerobic bacteria if symptoms suggest neutropenic colitis (i.e., typhlitis), other intestinal or intraabdominal athology, or perianal skin breakdown	Most infections are caused by beta-lactam susceptible Gram positive cocci, enteric Gram negative bacilli or other beta-lactam susceptible bacteria; *Pseudomonas* is less common but may cause severe infection and should be covered empirically in all cases Penicillin-resistant streptococci, MRSA, and MDR-GNB* may cause severe infection in specific situations Anaerobic bacteria are uncommon causes of infection, but should be treated in situations where infection with these bacteria are possible	Cefepime Piperacillin/tazobactam Meropenem Add vancomycin in specific situations when infection with a beta-lactam resistant Gram positive coccus is suspected Add a second agent effective against Gram negative bacilli (e.g., aminoglycoside, quinolone) or use meropenem in specific situations when infection with a drug-resistant Gram negative bacillus is suspected Add metronidazole or use piperacillin/tazobactam or meropenem when infection with anaerobic bacteria is suspected

Condition	Recommendation	Rationale	Examples of antibiotics that could be used
Prolonged fever (e.g., ≥5 days) and neutropenia, despite broad-spectrum antimicrobial therapy	Empiric treatment regimens as described for fever and neutropenia plus antifungal therapy	*Candida*, in particular, but also mold infection may occur	Empiric treatment for fever and neutropenia plus fluconazole or another azole caspofungin. micafungin, or anidulafungin liposomal amphotericin
Fever, presence of central venous catheter, and other risk factors for candidemia (parenteral nutrition, renal failure)	Empiric treatment regimens for no identified source plus antifungal therapy	Candidemia may cause severe sepsis	Empiric treatment for no identified source plus caspofungin, micafungin, or anidulafungin
Intra-abdominal infection, uncomplicated, community acquired	Empiric treatment regimens with enteric Gram negative aerobic and facultative bacilli and enteric streptococcal coverage plus obligate anaerobic bacilli coverage for distal small bowel, appendiceal, and colon-derived infection and for more proximal gastrointestinal perforations accompanied by obstruction or paralytic ileus	Aerobic and facultative Gram negative bacilli, enteric streptococci, and *Bacteroides* and other anaerobes are often co-pathogens	Ceftriaxone, ceftazidime or cefepime and metronidazole Piperacillin/tazobactam
Intra-abdominal infection, severe, hospital acquired or previously treated, compromised host, or inability to achieve adequate debridement or drainage	As above, plus enterococcal coverage and broader enteric Gram negative bacilli coverage	Enterococci and less than fully susceptible Gram negative bacilli may be co-pathogens	Piperacillin/tazobactam Meropenem

Condition	Recommendation	Rationale	Examples of antibiotics that could be used
Urinary tract infection, uncomplicated	Empiric treatment regimens with aerobic Gram negative coverage	Aerobic Gram negative bacilli are the common pathogens, enterococci are occasional pathogens	Gentamicin or ceftriaxone plus ampicillin if urine positive for Gram positive cocci
Urinary tract infection, complicated	Empiric treatment regimens with aerobic Gram negative, including *Pseudomonas*, and possibly *Candida* coverage	Aerobic Gram negative bacilli, including *Pseudomonas*, enterococcus and occasionally *Candida*	Ceftazidime, cefepime, piperacillin/tazobactam or meropenem (if colonized with multidrug resistant Gram-negative bacilli) Consider fluconazole, caspofungin or micafungin
Infection with MDR-GNB* (i.e., history of prior colonization/ infection, history of treatment with broad-spectrum agents, patient country of origin has high prevalence of MDR-GNB	**Consult infectious diseases**	Mechanisms of resistance among MDR-GNB are complex and require individual, specific treatment approaches	--

*MDR-GNB, multidrug resistant-Gram negative bacilli; MRSA, methicillin/oxacillin resistant *Staph. aureus*