Pediatric Pharmacy Advocacy Group

Broad Spectrum Antimicrobial Selection for Sepsis in Pediatric Intensive Care Units

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Disclosures

- I have no conflicts of interest to disclose

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Objectives

1. Utilize available literature and local antibiogram data to help create empiric antimicrobial regimens for sepsis in the pediatric intensive care unit
2. Analyze risk factors for sepsis due to ESBL producing organisms
3. Analyze risk factors for fungal sepsis in the pediatric intensive care setting

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Site of Infection with Severe Sepsis in Pediatric Patients

1. Respiratory diseases: 25-50%
2. Bloodstream infection: 18-68%
3. Genitourinary system- ~5-22%
4. Others less common than above
   - Abdominal: ~ 5-8%
   - Device related: ~4-9%
   - CNS (most common < 1 year): < 4%
   - Unknown- 7% - ~ 45%

- Ranges due to differences between studies

Ruth, et al. *Pediatr Crit Care Med.* 2013; 14:686–693.
Hartman, et al. *Pediatr Crit Care Med.* 2013; 14:686–693.

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Comorbidities in Pediatric Patients with Sepsis

- At least one: 74%
  - Respiratory: 7-30%
  - Cardiovascular: ~25%
  - Hematologic/oncologic/malignancy: 24-34%
  - Neurologic: 26%
  - Metabolic: 20-13%
  - Gastrointestinal: 5-25%

Ruth, et al. *Pediatr Crit Care Med.* 2013; 14:686–693.
Hartman, et al. *Pediatr Crit Care Med.* 2013; 14:686–693.

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Severe Sepsis Mortality Rates

- Adults
  - United States: 12-21%
  - Australia/New Zealand: 24%
  - Highest in elderly with comorbidities
- Children
  - United States: 9-14.4%
  - Worldwide: 25%

PROCESS. *N Engl J Med.* 2014;370:1683-93.
Miller, et al. *Am J Respir Crit Care Med.* 2013;188:77–82.
Ruth, et al. *Pediatr Crit Care Med.* 2013; 14:686–693.
Weiss, et al. *Am J Respir Crit Care Med.* 2015;191(10):1147–1157.
Hartman, et al. *Pediatr Crit Care Med.* 2013; 14:686–693.

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Children Most at Risk for Mortality in Severe Sepsis- US data 2004 or Later

- Independent risk factors
  - Underlying Hematologic/oncologic condition and cardiac disease: ~20% incidence, 1.4-2 higher odds
  - Infants < 1 year: 10-19%, 1.4 higher odds
- Bacteremia, endocarditis, CNS infection, device related: 11-17% (higher than SSTIs and UTIs)
- Fatality after mechanical ventilation 2 times higher
- Fungal and meningococcal: ~9-21% (highest among possible pathogens)

Ruth, et al. *Pediatr Crit Care Med.* 2013; 14:686–693.
Hartman, et al. *Pediatr Crit Care Med.* 2013; 14:686–693.

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Sepsis Related Guidelines Available

- Sepsis targeted guidelines
  - Davis, et al. 2017: Most recent, pediatric, but not antimicrobial focused
  - Rhodes, et al. 2017: Most recent, but adult focused Sepsis Guidelines
  - Dellinger, et al. 2013: Older guideline, but intent was to be applied to pediatric patients also
- Indication specific guidelines related to sepsis:
  - Tunkel, et al. 2017: Healthcare Associated Ventriculitis and Meningitis
  - Pappas, et al. 2016: Candidiasis including some pediatrics
  - Baltimore, et al. 2015: Endocarditis in childhood
  - Bradely, et al. 2011: Community Acquired Pneumonia in Children
  - Solomkin, et al. 2010: Intra-abdominal infections including children
  - Solomin, et al. 2010: Adults HAP/VAP guidelines
  - Mermel, et al. 2009: Catheter-related blood stream infections, includes pediatric recommendations
  - Tunkel, et al. 2004: Community Acquired Meningitis

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Sepsis Focused Guidelines

- 2016/17 Surviving Sepsis Guidelines (Pediatric guidelines to be published separately)
  - Recommend empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens (including fungal/viral)
  - Narrowing of agents when identification and sensitivities are available or adequate clinical response
  - Recommend against combination treatment, but also state that several days “is biologically plausible and likely to be clinically useful”

Rhodes, et al. *Intensive Care Med.* 2017;43:304-377.

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Antimicrobials Mentioned in Adult Guidelines

- Most often used are carbapenems and beta-lactam/beta-lactamase inhibitors (e.g., piperacillin/tazobactam)
  - Rationale: Most adult patients with sepsis/septic shock have some form of immunocompromise and so regimens should cover hospital associated infections
- If MRSA risk factors present, vancomycin or teicoplanin
- Antimicrobial restriction not appropriate for this patient population

Rhodes, et al. *Intensive Care Med.* 2017;43:304-377.

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Controversy of Adult Guidelines

- IDSA did not endorse the guidelines
  - Verbiage regarding choices thought to be confusing
  - Concerns regarding patients with suspected sepsis being treated like severe sepsis patients
  - Evidence regarding combination therapy not sufficient to warrant broad usage
- Combination therapy
  - Not a definitive recommendation
- Concerns regarding universal implementation
  - Could lead to patients without an infection receiving unnecessary broad-spectrum antimicrobials

IDSA Sepsis Task Force. *Clin Infect Dis.* 2018;66(10):1631-1635.

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SO WHAT ARE BEST PRACTICES FOR PEDIATRIC SEPSIS AND WHAT MAY CHANGE PRACTICE BETWEEN INSTITUTIONS?

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Pediatric Sepsis Related Guidelines

- Pediatric Hemodynamic Shock Guidelines
  - Antimicrobial administration is step 4 of first-hour process
- 2012/13 Surviving Sepsis Guidelines include Pediatric specific recommendations
  - Adult antimicrobial recommendations differ slightly from updated version regarding verbiage, but minimal mention of specific drugs
  - In Pediatrics, should base targeted therapy on epidemic or endemic infections and patient scenario
    - H1N1 Influenza, MRSA, penicillin-resistant *S. pneumoniae*
    - Neutropenia, history of PICU admission
  - Use of clindamycin for anti-toxin effects recommended for toxic shock syndromes with refractory hypotension

Rhodes, et al. *Intensive Care Med.* 2017;43:304-377.
Dellinger, et al. *Intensive Care Med.* 2013;39:165–228.

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Empiric Regimens and De-Escalation

- All guidelines recommend de-escalation to narrowest option if a pathogen is known
  - Helps with preventing future infections due to resistant organisms
  - ~1/3 of patients with sepsis do not have a causative pathogen identified making de-escalation difficult
- Appropriate empiric therapy is vital for efficacy and also is helpful when de-escalation is difficult due to lack of a definitive pathogen

Rhodes, et al. *Intensive Care Med.* 2017;43:304-377.
IDSA Sepsis Task Force. *Clin Infect Dis.* 2018;66(10):1631-1635.
Dellinger, et al. *Intensive Care Med.* 2013;39:165–228.

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What are Relevant Pathogens to Cover in an Empiric Regimen?

- Broad categories
  - Bacteria: Gram +, gram -, atypical, anaerobic
  - Fungal: Usually only in at risk patients
  - Viruses: Influenza most likely to cause severe sepsis, HSV and CMV potentially for neonatal period
- Depends on multiple factors
  - Location of acquisition: Outpatient, inpatient, ICU
  - Presenting symptoms/potential source of infection
  - Underlying risk factors

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Non-viral Causes of Overall Pediatric Severe Sepsis- After 2004

- Gram positive: ~12.5-23%
  - *S. aureus:* 7-10%
  - *Streptococcus spp*: 3.3-6.4% (*GBS* 0.4%, *S. pneumoniae* 0.8%)
  - *Enterococcus spp: 4.8%*
- *Gram negative:* ~ 8.8%-16.5%
  - *E. Coli:* 2.5-4.4%
  - *Klebsiella spp:* 3.4-4.4%
  - *Enterobacter spp: 3.3%*
  - *P. aeruginosa:* 2.5-3.2%
  - *H. influenzae:* 0.4-1.2%
- Fungal: 4.4-5.3% (majority *Candida spp*)
- *Coagulase negative staphylococcus (CoNS)*- Most common, but potentially a contaminant outside of the neonatal period

Ruth, et al. *Pediatr Crit Care Med.* 2013; 14:686–693.
Hartman, et al. *Pediatr Crit Care Med.* 2013; 14:686–693.
Larru, et al. *Pediatr Infect Dis J.* 2016;35:507–510.

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What is a Broad Spectrum Empiric Pediatric Antimicrobial Regimen?

- Depends on multiple factors
  - Location of infection and likely pathogenic organisms
  - Local susceptibilities
- Differentiating coverage concepts for bacterial pathogens
  - Gram +: MSSA, MRSA, *enterococcus spp.*, vancomycin-resistant *enterococcus spp.*, penicillin resistant *S. pneumoniae*
  - Gram -: *M. catarrhalis*, *H. influenzae, E. coli/Klebsiella spp,* inducible *AMP-C* producing *Enterobacteriaceae*, *ESBL Enterobacteriaceae*, *P. aeruginosa,* and multidrug resistant organisms
  - Anaerobic (oral and GI)*, B. fragilis*
  - Atypical pneumonia pathogens

Gerber, et al. *Infect Control Hosp Epidemiol.* 2017;38:993–997

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Pediatric "Broad Spectrum" Agents

- Most relevant medications ranked starting with the broadest spectrum of activity **based solely** on number of relevant and common pediatric pathogens covered (n=14 pathogens from previous slide):

1. Meropenem
2. Levofloxacin
3. Piperacillin/tazobactam, ciprofloxacin, ceftaroline
4. Linezolid, cefepime, amoxicillin/clavulanate, ampicillin/sulbactam, amikacin
5. Ceftriaxone, vancomycin, tobramycin/gentamicin, colistimethate, daptomycin
6. Sulfamethoxazole/trimethoprim, ceftazidime, azithromycin, clindamycin

- Think "collateral damage" if used inappropriately

Gerber, et al. *Infect Control Hosp Epidemiol.* 2017;38:993–997.

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Applying Coverage Concepts to Particular Disease States

- What is the type of infection and what are the most common organisms?
- Do any underlying disease states increase the risk of certain types of organisms?
- Was the infection acquired inpatient vs. outpatient?
- What are the local susceptibilities at the institution?

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Patient Case

- A 4-year-old M was admitted 2 weeks ago after an ATV accident in a wooded area resulting in a collapsed lung with multiple deep lacerations on his chest and abdomen
- Multiple abdominal and thoracic surgeries have occurred to remove necrotic lung and some bowel (most recent 7 days ago), and some of thoracic cavity was unable to be closed at this time
- Finished 14 days of ceftriaxone and metronidazole yesterday for thoracic wound infections and likely intra-abdominal abscess
- Prior thoracic wound cultures have grown mixed organisms including *E. Coli* and *MSSA*
- He is mechanically ventilated, has a central line, a foley catheter, and is also receiving TPN
- Today has a fever of 38.5°C, elevated WBC and CRP, (CRP has been elevated since admission), some decreased in ventilator settings, but his blood pressure has been stable
- The team is getting cultures from his central line, foley, and his open wound and ordering a chest X-ray and abdominal ultrasound

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Questions Relevant to Determining Empiric Therapy

- What are (if any) risk factors for resistant gram-positives?
- What are risk factors (if any) for resistant gram negatives?
- What are risk factors (if any) for fungal infections?
- What would be a reasonable empiric antimicrobial regimen?

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Potential Role of Combination Therapy for Gram Positives

- Recommended in multiple disease specific guidelines and for pediatric patients
  - Strength of recommendations usually weak/low quality of evidence
- Empirically
  - Clindamycin: Recommended in 2013 sepsis guidelines for pediatric patients with toxin mediated gram + infections
- Definitive treatment for specific organisms
  - Endocarditis- gentamicin synergy, rifampin if prosthetic devices
  - Meningitis- rifampin for gram positive infections with external devices, gentamicin could also be considered (IV/IT)

Rhodes, et al. *Intensive Care Med.* 2017;43:304-377.
Dellinger, et al. *Intensive Care Med.* 2013;39:165–228.
Baltimore, et al. *Circulation.* 2015;132:1487-1515.
Tunkel, et al. *Clin Infect Dis.* 2017;64(6):e34–e65.

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Double Coverage for Gram Negatives

- Concept: To provide empiric coverage for multi-drug resistant pathogens by using two different drugs that may cover such pathogens
- Impact on mortality most described in bacteremic adults with *P. aeruginosa, S. maltophilia* and *Acinetobacter spp.*
- Choice of agents if used
  - Usually β-lactam + (aminoglycoside or fluoroquinolone): NOT recommended to use two β-lactams or two intracellular agents

Rhodes, et al. *Intensive Care Med.* 2017;43:304-377.
Dellinger, et al. *Intensive Care Med.* 2013;39:165–228.

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Deciding if Double Coverage is Needed

- At risk for a multi-drug resistant gram negative
  - Immunosuppression, hospital acquired
- Local institutional susceptibilities
  - No set standard, >10% threshold has been recommended in some disease states
- Life threatening nature of the possible infection
- Comorbid disease states increasing the chance of toxicity
  - Aminoglycoside may be more harmful if patient has acute kidney injury

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Potential Role of Combination Therapy for Treatment of a Gram Negative

- Sepsis guidelines (Adult data)
  - A prospective randomized study did not show a benefit and increased harm, but meta-regressions suggest benefit in severely septic patients, but harm in milder sepsis
  - Strong recommendation to NOT use in neutropenia
  - Summary of guidelines: **Not a standard recommendation**, but biologically plausible in some scenarios
- Pediatric retrospective study for *Enterobacteriaceae* bacteremia
  - No improvements in outcomes (time to negative culture, mortality)
  - Co-infection: Only independent predictor of time to cure

Rhodes, et al. *Intensive Care Med.* 2017;43:304-377.
Berkowitz, et al. *Pediatr Infect Dis J.* 2015;34:1203-6.

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Risk Factors For Third Generation Cephalosporin Resistant Enterobacteriaceae in Pediatrics

- Surveillance Network Database 1999-2011
  - ICU admission (2.9% ESBL), floor patients (1.1%) and outpatient (0.29%)
  - Blood and respiratory (~3.5 % ESBL), urine (0.3% ESBL rate but has the largest number of ESBL isolates)
- Independent risk factors
  - Neurologic and gastrointestinal comorbidities
  - Receipt of 3rd generation cephalosporins in the past 30 days, > 3 days of vancomycin exposure
  - Higher PRISM 1 scores
  - Foley catheter presence
  - Mechanical ventilation

Logan, et al. *J Pediatric Infect Dis Soc.* 2014;3(4):320-8.
Logan, et al. *J Pediatric Infect Dis Soc.* 2014;3:312-19.
Benner, et al. *J Pediatr Pharmacol Ther.* 2014;19(2):83–90.

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SPECIFIC DISEASE STATES

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PICU Central Line Infection Causes- Based on Overall Causative Pathogens

- Gram positive
  - *CoNS:* 20.9%
  - *S. aureus:* 18.1%
  - *E. faecalis:* 9.1%
  - *E. faecium: 2%*
- Gram negative
  - *K. pneumoniae/oxytoca*: 9.4%
  - *E. coli*: 7.4%
  - *Enterobacter spp*: 5.5%
  - *P. aeruginosa*: 3.4%
  - *Acinetobacter spp:* 1.1%
- *Candida* (total 8%)
  - *Albicans: 3.3%*
  - *Parapsilosis: 2.3%*

Lake, et al. *Infect Control Hosp Epidemiol. 2018;39:1–11.*

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Central Line Infections - Guidelines

- Intended to apply to Pediatrics also
- Empiric recommendations- severely ill sepsis
  - Vancomycin if *MRSA* prevalence is high in the area (linezolid not recommended)
  - Gram negative coverage should be based on local susceptibility data and severity of disease
    - 4th generation cephalosporin or carbapanem, or piperacillin/tazobactam
    - Empiric coverage with two gram-negative agents if neutropenic, patient with sepsis, or patient colonized until the culture results

Mermel, et al. *Clin Infect Dis*. 2009;49(1):1-45.

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PICU Central Line Infection Causes- Susceptibilities

- Gram positive
  - *MRSA:* 30.6%
  - *E. faecalis:* 0.2% VRE
  - *E. faecium:* 57% VRE, 71% ampicillin resistant
- Gram negative
  - *K. pneumoniae/oxytoca*: 5.5% MDR
  - *E. Coli*: 5.2% MDR
  - *Enterobacter spp*: 3.7% MDR
  - *P. aeruginosa*: 8.1% MDR
  - *Acinetobacter:* 8.6% MDR
- *Candida*
  - *Albicans: 1.4%* fluconazole resistance
  - *Parapsilosis: 0%* fluconazole resistance
  - Others: 11.5% fluconazole resistance

Lake, et al. *Infect Control Hosp Epidemiol. 2018;39:1–11.*

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Pneumonia Coverage Concepts

- Community-acquired, reasonably healthy patient in the PICU
  - Consider influenza when in season and based on PCR results: Oseltamivir X 5 days (extended durations have been reported)
  - Ceftriaxone considered broad (covers *MSSA,* high MIC *S. pneumoniae, H. influenzae all types),* recommended in guidelines for "life-threatening" infections (e.g., empyema)
    - High dose ampicillin first line on floor patients and could be considered in the PICU based on severity and immunizations

Bradley, et al. *Clin Infect Dis. 2011;53(7):e25–e76.*

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Other Antimicrobials for Community Acquired Pneumonia

- Empyema/parapneumonic effusions
  - *S. aureus* coverage and *MRSA* if prevalent in area or of concern (only 1% of pneumonias)
  - *S. aureus* with influenza disease or *S. pyogenes/S. aureus* with possible toxins, consider clindamycin
- Atypicals
  - Reasonable to cover for if in the ICU
  - PCR testing can help guide this treatment

Bradley, et al. *Clin Infect Dis.* 2011;53(7):e25–e76.
Jain, et al. *N Engl J Med.* 2015;372:835-45.
Randolph, et al. *Clin Infect Dis.* 2019;68(3):365-372.

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Ventilator Associated Pneumonia Pathogens

- Higher percentages of highly resistant organisms compared to bacteremia (*P. aeruginosa* also high in UTIs)
  - *S. aureus:* 24.1%
  - *P. aeruginosa:* 15.7%
  - *Enterobacter spp*: 10.2%
  - *K. pneumoniae/oxytoca*: 12.2%
  - *Serratia spp*: 4.7%
  - *Acinetobacter spp*: 3.5%

Lake, et al. *Infect Control Hosp Epidemiol. 2018;39:1–11.*

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Hospital Acquired Pneumonia and Ventilator Associated Pneumonia

- No pediatric specific guidelines, adult guidelines:
  - *P. aeruginosa* and *S. aureus* coverage likely needed, maybe justified by surveillance statistics in the PICU
    - If >10-20% MRSA in institution, vancomycin recommended
    - Ventilated patients with HAP or septic shock- consider *P. aeruginosa* coverage with 2 antibiotics if resistance in unit is >10% for agent to be used
- Aspiration pneumonia
  - Anaerobic coverage for oral flora needed
  - Clindamycin, ceftriaxone, or ampicillin/sulbactam are appropriate options
  - Coverage included in some antipseudomonal agents

Kalil, et al. *Clin Infect Dis.* 2016;63(5):e61–111.

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VAP Organism Susceptibilities- National Surveillance Network

- *MRSA:* 30.5%
- *P. aeruginosa:* 11.2% MDR
- *Enterobacter spp*: 20.8% 3rd generation resistant
- *K. pneumoniae/oxytoca*: 22.2% resistance to 3rd-4th generations cephalosporins, 6.7% MDR

Lake, et al. *Infect Control Hosp Epidemiol. 2018;39:1–11.*

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Intra-Abdominal Infections

- Community acquired
  - 3rd-4th Generation Cephalosporin + metronidazole
  - OR a single drug regimen with anaerobic coverage (e.g., meropenem, piperacillin/tazobactam, ticarcillin/clavulanate)
  - *P. aeruginosa* coverage may not be necessary (e.g., perforated appendicitis) unless confirmed infection or high local prevalence
- Hospital acquired
  - Regimen should include *P. aeruginosa* and anaerobic coverage
- Clindamycin NOT recommended due to *B. fragilis* resistance for either location of acquisition

Solomkin, et al. *Clinical Infectious Diseases.* 2010; 50:133–64.

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Determination of Extended Coverage for Hospital Acquired Intra-abdominal Infections

- <20% resistance to ESBL enterobacteriaceae, *P. aeruginosa*, or other multi-drug resistance
  - Can use ceftazidime/cefepime + metronidazole
- >20%: piperacillin/tazobactam or meropenem
- MRSA coverage
  - If inpatient acquired, likely colonized, or significant antibiotic exposure

Solomkin, et al. *Clinical Infectious Diseases.* 2010; 50:133–64

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Meningitis

- Community acquired
  - Vancomycin and ceftriaxone usually considered appropriate coverage outside of the neonatal period
  - Combination targets resistant *S. pneumoniae*
- Healthcare associated (e.g., CNS devices or procedures)
  - Vancomycin + (Ceftazidime, cefepime, or meropenem) based on local susceptibilities
  - Intrathecal administration may be used (not penicillins or cephalosporins due to neurotoxicity)
- Combination therapy with aminoglycosides for *Enterococcus* species
- Rifampin also considered in patients with hardware in place

Tunkel, et al. *Clin Infect Dis*. 2004; 39:1267–84.
Tunkel, et al. *Clin Infect Dis*. 2017;64(6):e34–e65.

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Febrile Neutropenia in Hematologic/Oncologic Patients

- Empiric treatment- *P. aeruginosa* is a key pathogen to cover due to higher mortality
  - Cefepime or meropenem recommended
  - Only consider adding an additional agent if resistance is of concern, **clinically unstable**, or high local resistance (no threshold)
    - No evidence of improved outcomes in randomized studies
- Consider antifungal (echinocandin preferred), MRSA, anaerobic coverage if unstable or persistent fever

Lehrnbecher, et al. *J Clin Oncol. 2017;*35:2082-2094.

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When to Consider Fungal Infections

- Risk factors in pediatrics
  - Prolonged antibiotic exposure (possibly anaerobic activity)
  - > 3 days of vancomycin exposure
  - Parenteral nutrition
  - Bone marrow or solid organ transplant patients
  - Femoral catheterization
  - Malignancy related (AML, high-risk ALL, or relapsed acute leukemia, and children undergoing allogeneic HSCT, prolonged neutropenia, and high dose steroids)
- Prophylaxis with fluconazole?
  - In at risk patients: Surgical patients and mechanically ventilated patients
  - Only consider if local incidence NOT <5%

Mermel, et al. *Clin Infect Dis*. 2009;49(1):1-45.
Pappas, et al. *Clin Infect Dis*. 2016;62(4):e1–50.
Zaoutis, et al. *Clin Infect Dis*. 2010; 51(5):e38–e45.

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What Antifungals To Use

- Echinocandins generally preferred in ICU patients- although debatable CNS penetration
- Fluconazole can be considered if:
  - No prior exposure
  - Patient isn't colonized with resistant *Candida*
  - Also if there is a low occurrence of *C. krusei/glabrata*
- Amphotericin products are alternatives
- If molds/aspergillus suspected/identified, voriconazole/posaconazole should be considered
  - Severe trauma patients, sometimes seen in wartime

Mermel, et al. *Clin Infect Dis*. 2009;49(1):1-45.
Pappas, et al. *Clin Infect Dis*. 2016;62(4):e1–50.

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Other Possible Sepsis Causes

- Community acquired rickettsial diseases
  - Consider doxycycline- Rocky Mountain Spotted Fever can cause sepsis in some patients
    - Rash, altered mental status, and tick exposure
- Viral
  - Unlikely in non-neonates to cause sepsis, but CMV and HSV are possible if not altered mental status noted and patient not responding to antibiotics

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Strategies to Help Guide Appropriate Empiric Therapy

- Institutional guidelines utilizing institutional incidence/susceptibility rates based on common diseases
- Order sets for specific common indications
  - Could include algorithms stratifying treatment options based on risk factors

Lee, et al. *Pediatr Crit Care Med.* 2016; 17:187–193.

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Patient Case

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QUESTIONS??

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