## Anatomical

### Bone
- Septic Arthritis
- Osteomyelitis

### Central Nervous System
- Community Acquired Meningitis
- Nosocomial Meningitis

### Foot
- Diabetic Foot Infections

### Gastrointestinal
- Clostridium Difficile (CDI)
- Prophylaxis for UGI Bleeding

### Lung
- Acute exacerbation of COPD
- Hospital-acquired Pneumonia

### Skin
- Skin & Skin Structure Infections

### Vascular
- Central Line Infections

## Drug Use Guidelines

### β-Lactam Allergy

### Empiric Use of Antifungals

### Role of TMP-SMX

## Organism

### Candidemia (Yeast)

### Influenza

### PsA Single vs Double Coverage

### S. aureus Bacteremia
EMPIRIC CHOICE
- cefazolin 2 g iv q8h
- If high suspicion for Neisseria gonorrhoeae: ceftriaxone 2 g iv q24h
- If high suspicion for MRSA: vancomycin

DURATION
- Non-gonococcal: 2-4 weeks
- Gonococcal: 7-10 days

ALTERNATIVES FOR ALLERGIES
- See 1-page document on beta-lactam allergies:
  - cefazolin does not have a similar side chain to any other beta-lactam so can safely be used for patients with previous beta-lactam hypersensitivity reactions, except those with a previous reaction to cefazolin
  - ceftriaxone can safely be used in patients with previous beta-lactam hypersensitivity reactions EXCEPT those with a previous reaction to cefepime, cefotaxime or ceftriaxone
- Vancomycin can be used as an alternative for allergy in non-gonococcal septic arthritis
- For patients with gonococcal septic arthritis and beta-lactam allergy, consult ID for treatment recommendations

TOP ORGANISMS
- Staphylococcus aureus
- Streptococci
- Neisseria gonorrhoeae

CURRENT RESISTANCE ISSUES
- Fluoroquinolone resistant Neisseria gonorrhoeae are frequently encountered, therefore they are not a good empiric choice for gonococcal disease

IMMUNOCOMPROMISED HOST CONSIDERATION
- Same as for immunocompetent hosts

ADDITIONAL DIAGNOSTIC AND THERAPEUTIC COMMENTS
- Joint aspiration is almost always needed for diagnosis
- Orthopedic surgery consultation is usually required for
  a. diagnosis
  b. ensuring adequate joint drainage, and
  c. adjunctive therapy (e.g. role of splinting, physiotherapy, etc…)

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Acute Osteomyelitis

Antibiotics should be withheld until sterile tissue cultures are obtained, unless the patient is septic or there is a concomitant soft tissue infection. Identification of the causative organism is very important in order to treat appropriately.

EVALUATION
- Obtain sterile tissue cultures by percutaneous aspirate or surgical deep culture (ideally before starting antibiotics)
- Wound swabs tend to reflect colonization, and often do not indicate the infecting organism at the site of osteomyelitis
- If septic, draw blood cultures

EMPIRIC CHOICE
- For diabetic foot infections, refer to the 1-page document on that topic
- Acutely Unwell or Septic:
  - ceftriaxone 2 g iv q24h +/- metronidazole 500 mg p.o./iv q12h (add metronidazole for sacral osteomyelitis) +/- vancomycin (if known to be colonized/previous infection with MRSA)
  - if known to be ESBL colonized/previous infection: Meropenem 1 g iv q8h +/- vancomycin if known to be colonized/previous infection with MRSA
- Not septic:
  - Await sterile culture results to guide treatment

DURATION
- 4-6 weeks
- Shorter courses could be considered if the infected bone has been appropriately debrided

ALTERNATIVES FOR ALLERGIES
- If septic: meropenem 1 g iv q8h (penicillin cross-reactivity is ~ 1%) +/- vancomycin
- Not septic: await sterile culture results to guide treatment

TOP ORGANISMS
- Staphylococcus aureus
- Streptococci
- Gram negative bacilli
- Anaerobes

IMMUNOCOMPROMISED HOST CONSIDERATION
- Same as for immunocompetent host

ADDITIONAL DIAGNOSTIC AND THERAPEUTIC COMMENTS
- X-ray be normal for the first 2 weeks of osteomyelitis; use CT or MRI for diagnosis if suspicion is high but x-ray is negative

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COMMUNITY-ACQUIRED MENINGITIS

EMPIRIC CHOICE
- ceftriaxone 2 g iv q12h + vancomycin 25mg/kg iv loading dose x1 followed by 15 mg/kg iv q8h
- if over age 50, add ampicillin 2g iv q4h or TMP-SMX 5 mg/kg iv q6h

DURATION
- S. pneumoniae: 10 days
- N. meningitidis: 7 days
- L. monocytogenes: 21 days

ALTERNATIVES FOR ALLERGIES
- For non-anaphylactic penicillin allergy, ceftriaxone may be used.
- For severe β-lactam allergy, use moxifloxacin 400 mg iv q24h + vancomycin 15 mg/kg iv q8h (add agent for Listeria if over age 50 or immunocompromised (see below)).

TOP FIVE ORGANISMS (what we expect for common organisms)
- S. pneumonia
- N. meningitidis
- L. monocytogenes (esp. in those over age 50)
- aerobic Gram-negative bacilli

CURRENT RESISTANCE ISSUES
- The rate of ceftriaxone-resistant pneumococci in Toronto is <1%. Recommendations for treating with vancomycin are based, primarily, from jurisdictions with higher resistance than we are currently encountering in Toronto.

IMMUNOCOMPROMISED HOST CONSIDERATION (INCLUDING THOSE WITH ADVANCED LIVER/KIDNEY DISEASE)
- Add ampicillin 2 g iv q4h or TMP-SMX 5 mg/kg iv q6h for Listeria coverage.
- Fungal meningitis (esp. cryptococcal) is relatively common in those with severe cell-mediated immunocompromised (eg. steroids, transplantation).

ADDITIONAL DIAGNOSTIC AND THERAPEUTIC COMMENTS
- Dexamethasone 10mg iv q6h for 4 days (started as soon as possible prior to initiating antimicrobial therapy) is currently recommended. The current evidence demonstrates that this neither provides benefit nor harm in patients with bacterial meningitis (vis a vis mortality, neurologic sequelae), but a single study from the Netherlands suggested benefit and the recommendation remains controversial.
- Consideration for repeat lumbar puncture should be given for patients failing to improve after 24-48h of therapy.

References:


PREFACE

Infectious Diseases consultation strongly recommended for all cases of nosocomial meningitis

EMPIRIC CHOICES

Vancomycin 15-20 mg/kg iv q12h (with loading dose) PLUS one of:
  • ceftazidime 2 g iv q8h (or ceftriaxone 2 g iv q12h if basal skull fracture)
  • Adjunctive dexamethasone NOT routinely recommended

ROUTE

Intravenous (may consider p.o. step-down in cases caused by GNB susceptible to quinolones or TMP-SMX)

DURATION

Duration depends on multiple factors: 1) pathogen, 2) presence and removal of CSF shunt device, 3) presence of brain abscess, 4) presence of skull bone involvement (i.e., osteomyelitis), 5) clinical response to therapy
  • Meningitis
    - S. aureus – 14 days
    - Coagulase-negative staphylococci (CNST) – 7 days
    - Gram-negative bacilli – 21 days
  • Shunt infection – Device removal almost always required for clearance of organisms
    - CNST – 7 days minimum, continue 7 days beyond shunt removal
    - S. aureus – 14 days
    - GNB – 21 days

ALTERNATIVES FOR ALLERGIES

If severe beta-lactam allergy, vancomycin PLUS one of: ceftazidime or anti-pseudomonal quinolone

MOST COMMON ORGANISMS

• Staphylococcus species (including MSSA, MRSA and CNST)
• Pseudomonas aeruginosa
• Enteric gram-negative organisms (including broad-spectrum beta-lactamase producing organisms)
• Propionibacterium acnes
• Organisms associated with community-associated acute bacterial meningitis far less common

CURRENT RESISTANCE ISSUES

Local rates of ESBL and AMP-C producing organisms important in determining whether a carbapenem is indicated as initial therapy

IMMUNOCOMPROMISED HOST CONSIDERATION

Pathogens associated with community-associated bacterial meningitis also a consideration
• Consider addition of Listeria coverage (i.e., ampicillin or TMP-SMX) to empiric therapy

ADDITIONAL DIAGNOSTIC AND THERAPEUTIC COMMENTS

• Diagnosis based on clinical setting, CNS imaging, and cerebrospinal fluid (CSF) analysis (e.g., culture and cell counts)
• Organisms often considered to be non-pathogenic can be significant in nosocomial meningitis (e.g., CNST)
• Intra-ventricular antibiotics of unclear benefit and may be considered in cases with persistently positive CSF cultures or inability to remove CNS device

References:
DIABETIC FOOT INFECTIONS

*ID consultation recommended for mod-severe or complicated infections

**EMPIRIC CHOICES**
- **Not infected** – Do not treat (not all foot ulcers in diabetics are infected and absence of purulence or other features of inflammation make infection unlikely)
- **Cellulitis (without ulcer)** – cefazolin 1 g iv q8h or cephalexin 500 mg p.o. QID
- **Mild to Moderate** – cefazolin 1-2 g iv q8h or cephalexin 500 mg p.o. QID
- **Severe** – several options, choice depends on concern for MDR pathogens; choose one of following:
  - ceftriaxone + metronidazole
  - piperacillin-tazobactam 4.5 g iv q8h +/- vancomycin
  - meropenem +/- vancomycin
  - NB: vancomycin can be discontinued if patient is not colonized with MRSA
- **Chronic** – usually requires more formal evaluation to allow targeted therapy, ID consultation recommended

**ROUTE**
- Initial therapy intravenously if moderate to severe, oral step-down if improving and reliable oral option

**DURATION**
- Duration guided by clinical response, with shorter courses being sufficient for quick to respond infections
  - **Cellulitis** – 5-7 days
  - **Mild to Moderate** – 5-14 days
  - **Severe** – 7-14 days
  - **Underlying osteomyelitis** – 6 weeks

**DOSAGE ADJUSTMENTS**
- Concurrent renal disease is common, dosage adjustments depend on antimicrobial agent
- Higher doses (e.g., cefazolin 2 g q8h or cephalexin 750-1000mg p.o. qid) may be required for patients with elevated BMI (≥ 30)

**MOST COMMON ORGANISMS**
- **Mild to Moderate**
  - S. aureus, β-hemolytic streptococci
- **Severe or Chronic**
  - Gram-positives (e.g., S. aureus, β-hemolytic streptococci), Gram-negatives, anaerobes
  - Increased risk for resistant pathogens (e.g., MRSA, P. aeruginosa, MDR gram-negatives)

**CURRENT RESISTANCE ISSUES**
- Patients with chronic infections and multiple prior courses of antibiotics are more likely to have polymicrobial infections
- Patients colonized with resistant organisms (e.g., MRSA, ESBL/AMP-C producers) may require coverage for these pathogens; however, these organisms may simply colonize wound rather than cause infection

**IMMUNOCOMPROMISED HOST CONSIDERATION**
- Similar empiric coverage

**ADDITIONAL DIAGNOSTIC AND THERAPEUTIC COMMENTS**
- Superficial swabs of wound are **NOT** recommended and are prone to contamination with colonizing organisms
- When possible, sterile wound cultures should be obtained prior to starting antibiotics when multiple pathogens or osteomyelitis is suspected
- Imaging to confirm osteomyelitis – foot X-ray; MRI or bone/gallium scan if inconclusive; CT imaging may also be of benefit
- Management includes multidisciplinary approach: wound care and debridement as needed, pressure off-loading, chiropody, improved glycemic control, formal vascular evaluation of limb (+/- Vascular Surgery assessment)
- Infections in those with poor vascular supply may have higher rates of treatment failure with Abx alone

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# Table 1: Classification of severity and microbiological considerations in diabetic foot infection

<table>
<thead>
<tr>
<th>Severity</th>
<th>Characteristics</th>
<th>Common causative pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild</strong></td>
<td>Local signs of inflammation in the absence of systemic signs and symptoms</td>
<td>Aerobic gram-positive cocci</td>
</tr>
<tr>
<td>Local infection involving epidermis and subcutaneous tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>Local signs of inflammation with erythema &gt; 2 cm in the absence of systemic signs</td>
<td>Acute, less extensive: aerobic gram-positive cocci, Chronic, more extensive: gram-positive and gram-negative organisms, anaerobes</td>
</tr>
<tr>
<td>Infection involving tissue deeper than epidermis and subcutaneous tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td>Hemodynamic compromise, metabolic disturbances (severe hyperglycemia, new onset renal insufficiency)</td>
<td>Gram-positive organisms (including MRSA), gram-negative organisms, anaerobes</td>
</tr>
<tr>
<td>Local infection with signs of systemic inflammatory response syndrome*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Special considerations</strong></td>
<td>Exposure to antibiotic agents in the previous 1 mo</td>
<td>Gram-negative bacilli</td>
</tr>
<tr>
<td></td>
<td>Previous history of MRSA infection or colonization within the last year, high local prevalence of MRSA, severe infection or prolonged wound</td>
<td>MRSA</td>
</tr>
<tr>
<td></td>
<td>Frequent exposure to water, high local prevalence, warm climate</td>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
</tbody>
</table>

Note: MRSA = methicillin-resistant *Staphylococcus aureus*.  
*The presence of more than 2 of the following signs and symptoms: temperature higher than 38°C or lower than 36°C; heart rate faster than 90 beats/min; respiratory rate faster than 20 breaths/min; partial pressure of carbon dioxide less than 32 mm Hg; leukocyte count greater than 12 or less than 4 cells/ml, or more than 10% bands.

References:


Consult ID in cases of severe, complicated, or multiply recurrent CDI.

**EMPIRIC CHOICE**
- **Step 1:** Stop any unnecessary antimicrobials.
- **Step 2:** Empiric antimicrobial selection depends on severity of infection (Table 1).

**ROUTE / DOSE**

<table>
<thead>
<tr>
<th>Clinical Definition</th>
<th>Supportive Clinical Data</th>
<th>Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode, mild/moderate</td>
<td>No features of severe CDI.</td>
<td>metronidazole 500 mg p.o. TID x 14 days (alternatively 250 mg p.o. QID if GI intolerance).</td>
</tr>
<tr>
<td>Initial episode, severe</td>
<td>Leukocytosis with a wbc ≥ 15, or a SrCr ≥ 1.5x's premorbid level.</td>
<td>vancomycin 125 mg p.o. 4 times daily x 14 days.</td>
</tr>
<tr>
<td>Initial episode, severe, complicated</td>
<td>Hypotension or shock, ileus, megacolon</td>
<td>vancomycin 125 mg p.o./mg 4 times daily PLUS metronidazole 500 mg iv every 8 hours. If complete ileus consider adding intra colonic vancomycin.</td>
</tr>
<tr>
<td>First recurrence</td>
<td></td>
<td>Same as initial episode, mild/moderate#</td>
</tr>
<tr>
<td>Second recurrence</td>
<td></td>
<td>vancomycin in a tapered/pulsed regimen.</td>
</tr>
</tbody>
</table>

Table 1: Recommendations for the Treatment of CDI (Adapted from Table 3 Infection Control & Hospital Epi. May 2010:31(5)).

- Early surgical intervention is key. Intracolonic vancomycin in to be considered last line adjunctive therapy only.
- Solution is supplied by pharmacy as 5 grams in 100 mL amber plastic or glass bottle (Final concentration of 500 mg per 10 mL). Each dose of 500 mg = 10 mL must be further diluted as instructed in the administration section. See UHN Nursing administration policy for intra colonic vancomycin.
- Consider referral to fecal transplant study.
- Some experts prefer vancomycin, but the choice to do so must also consider the high cost of the drug (especially to those being discharged from the hospital) and the lack of evidence supporting vancomycin over metronidazole in this setting.

**DURATION**

- For most cases, 14 days of therapy is adequate however, longer durations may be required for severe or recurrent infection. This decision should be made in consultation with infectious diseases.

**ALTERNATIVES FOR ALLERGIES**

- Consult ID

**IMMUNOCOMPROMISED HOST CONSIDERATION**

- Except for instances of febrile neutropenia, treatment of CDI in immunocompromised hosts is not automatically considered ‘complicated’. Patients should be assessed on a case by case basis based on risk factors and disease severity. Consult infectious diseases.

**ADDITIONAL DIAGNOSTIC AND THERAPEUTIC COMMENTS**

- Early surgical intervention should be considered in cases of severe CDI.
- There is no evidence to support test for cure by repeating *C. difficile* testing. Spores may remain for some time and consequently *C. difficile* test may remain positive 6-8 weeks or longer in some cases.
- Avoid antiperistaltic agents.
- Avoid proton pump inhibitors unless indicated.
- There is no evidence to support long term antimicrobial prophylaxis for CDI.
References


Antibiotic Prophylaxis in Upper GI Bleeding

EMPIRIC CHOICE

✦ ceftriaxone

ROUTE

✦ iv

DOSE

✦ 1g

DURATION

✦ 3 days

ALTERNATIVES FOR ALLERGIES

✦ ertapenem 1g iv daily

TOP FIVE ORGANISMS (what we expect for common organisms)

✦ Enterobacteriaceae (responsible for ~80% of infections)

CURRENT RESISTANCE ISSUES

✦ Many patients have been exposed to fluoroquinolones, and so there is a significant risk of quinolone-resistant enterobacteriaceae in such patients.

ADDITIONAL DIAGNOSTIC AND THERAPEUTIC COMMENTS

✦ Although not definitive, the burden of evidence demonstrates a benefit of antibiotic prophylaxis in upper GI bleeding in patients with cirrhosis (and presumed variceal bleeding). However, the benefit is seen in all patients with cirrhosis, regardless of the presence or absence of ascites.
✦ Antibiotic prophylaxis appears to reduce bacteremia, pneumonia, SBP and urinary tract infections in this setting.
✦ Many references recommend 2 g of ceftriaxone. The evidence does not support the need for this.

References:


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Treatment of Acute Exacerbation of COPD with antimicrobials is controversial. The MSH-UHN ASP does not endorse routine treatment of AECOPD with antimicrobials.

However, if the decision to use antibiotics is made:

**EMPIRIC CHOICE**
- ceftriaxone 1g iv daily or amoxicillin-clavulanate 875/125 mg p.o. BID

**DURATION**
- 7 days

**ALTERNATIVES FOR ALLERGIES**
- moxifloxacin 400 mg p.o./iv daily

**TOP FIVE ORGANISMS (what we expect for common organisms)**
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Moraxella catarrhalis*

**CURRENT RESISTANCE ISSUES**
- Consider the patients’ antibiotic exposure in the previous 3 months
- Proportion of *H.influenzae* resistant to ampicillin/amoxicillin in 2008-2009\(^1\): ~ 20%
- *Streptococcus pneumonia* resistance rates from Ontario and Toronto labs 2010-2011\(^2\):
  - penicillin G (non-meningitis breakpoints) 0.4%
  - ceftriaxone 0.7%
  - moxifloxacin 1%
  - levofloxacin 1.9%
  - amoxicillin 4.5%
  - doxycycline 16%
  - azithromycin/clarithromycin 28%

**IMMUNOCOMPROMISED HOST CONSIDERATION**
- None

**References**
- Data courtesy of Dr. Donald Low from Ontario laboratories that submitted data to the Canadian Bacterial Surveillance Network
- Data courtesy of Dr. Allison McGeer from adult respiratory specimens from Ontario laboratories participating in the CBSN/TIBDN, 2010-2011.
**EMPIRIC CHOICE**

- Patient is on a non-ICU ward: ceftriaxone 1g iv q24h or amoxicillin-clavulanate 875/125 mg p.o. BID
- Patient is in the ICU or transferred there as a result of HAP:
  - piperacillin-tazobactam 4.5 g iv q8h
  - Could consider ceftriaxone instead of piperacillin-tazobactam for some patients in whom the risk of *Pseudomonas* is likely low, such as patients who have been on a ward where *Pseudomonas* infections are uncommon or those that have been in the hospital for ≤ 1 week
  - If known to be colonized with MRSA, add vancomycin
  - If known to be colonized with an ESBL, use meropenem 1g iv q8h instead of piperacillin-tazobactam

**DURATION**

- 7 days

**ALTERNATIVES FOR ALLERGIES TO BETA-LACTAMS**

(see 1-pager on beta-lactam allergies for risk of cross-reactivity)

- Patient is on a non-ICU ward: moxifloxacin 400 mg p.o./iv q24h
- Patient is in the ICU or transferred there as a result of HAP:
  - moxifloxacin 400 mg p.o./iv q24h if infection due to *Pseudomonas* is likely to be low
  - If *Pseudomonas* risk is high: meropenem 1 g iv q8h (cross-reactivity is 1% with penicillin allergy)
  - If known to be colonized with MRSA, add vancomycin

**TOP ORGANISMS**

(*what we expect for common organisms*)

- *Staphylococcus aureus*
- Gram negative aerobic bacilli (Klebsiella, Serratia, Pseudomonas, etc)
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*

**CURRENT RESISTANCE ISSUES**

- Consider the patient’s prior antibiotic use and colonization status (ie. ESBLs, MRSA) in making your empiric decision

**IMMUNOCOMPROMISED HOST CONSIDERATION**

- piperacillin-tazobactam 4.5 g iv q8h
- Treat x 10 days

**ADDITIONAL DIAGNOSTIC AND THERAPEUTIC COMMENTS**

- Antimicrobial therapy is not indicated for aspiration pneumonitis (primarily from macro-aspiration from vomiting).
- Aspiration pneumonia (primarily from swallowing difficulties) does not require the addition of metronidazole as the anaerobes involved are oral anaerobes (ie. Peptostreptococcus) which are covered by most beta-lactams

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EMPIRIC CHOICE

- Uncomplicated cellulitis (with or without abscess; includes erysipelas): cephalexin 500 mg p.o. QID
- Complicated cellulitis (SSSI severe enough to cause hospitalization): cefazolin 1 g iv q 8 h
- Suspected CA-MRSA cellulitis (assessment based on risk factors):
  - Uncomplicated: TMP/SMX DS 1 tab p.o. bid + cephalexin 500 mg po QID
  - Complicated: vancomycin 15 mg/kg iv q 12 h
- Cellulitis in known MRSA colonized patient: as per MRSA susceptibility

ROUTE

- Uncomplicated cellulitis: oral
- Complicated cellulitis: intravenous –if clinically improving, step down to oral after 24-48 hours

DURATION

- Uncomplicated cellulitis: 5 days
- Complicated cellulitis: 7-10 days

ALTERNATIVES FOR ALLERGIES

- Oral: Clindamycin or quinolone – TBA (as per LHIN document)
- IV: Vancomycin 15 mg/kg IV q 12 h

TOP FIVE ORGANISMS (what we expect for common organisms)

- Group A Streptococci – more likely causative organism in non-purulent SSSIs
- Staphylococcus aureus – more likely causative organism in purulent SSSIs
- MRSA
- Other Streptococcus spp.

CURRENT RESISTANCE ISSUES

- MRSA accounts for approximately 25% of all S. aureus isolates in Canada (CANWARD surveillance data)
- Avoid clindamycin in suspected CA-MRSA infections as risk of inducible resistance
- GAS remains 100% susceptible to penicillin

IMMUNOCOMPROMISED HOST CONSIDERATION

- Gram negatives including Pseudomonas should be considered if not improving on standard Rx OR if ecthyma gangrenosum – add ciprofloxacin or change to ceftazidime
- Consider fungal etiologies if associated skin lesions or if fail to respond to antibiotics after 1 week; suggest diagnostic biopsy

ADDITIONAL DIAGNOSTIC AND THERAPEUTIC COMMENTS

- Blood cultures may assist management in immunocompromised and clinically unstable patients
- Abscess without surrounding cellulitis may be cured with lancing (I&D: send for C+S) alone and no antibiotics
- For non-resolving cellulitis or if concerned about exposure related cellulitis (ie. bites, water), consult ID

References:

IDSA SSSI guidelines
Archives Int Med (JAMA Internal Medicine) 2004; 164(15): 1664-74
Central Line Infections

EMPIRIC CHOICE
- Clinically stable short or long-term catheters: vancomycin
- Septic patients: pip-tazo* 4.5 g IV q 8 h + vancomycin

ROUTE
- Intravenous

DURATION
- Generally 7-14 days, but dictated by organism and presence of complications.
  - CNST in stable patient with short-term catheter: remove catheter and stop empiric vancomycin once organism identified; monitor for clinical improvement
  - CNST in patient with clinical line sepsis: remove catheter and continue vancomycin for 5 days
  - Staphylococcus aureus infection in long-term catheter requires minimum 14 days therapy
  - Complications such as infective endocarditis, suppurative thrombophlebitis or osteomyelitis require prolongation of antibiotics to 4-6 weeks.

ALTERNATIVES FOR ALLERGIES
- linezolid 600 mg iv/p.o. q 12h to replace vancomycin. Consult ID

TOP FIVE ORGANISMS (what we expect for common organisms)
- Coagulase negative Staphylococci
- Staphylococcus aureus
- Enterococci
- Candida albicans
- Gram negative bacilli (including Pseudomonas aeruginosa in ICU and hemodialysis patients)

CURRENT RESISTANCE ISSUES
- MRSA accounts for approximately 15% of S. aureus blood isolates
- Gram negative susceptibility to pip-tazo in blood isolates from MSH/UHN ICUs 78-100%; aminoglycosides can be considered as alternative

IMMUNOCOMPROMISED HOST CONSIDERATION
- Consider adding gram negative coverage, including Pseudomonas aeruginosa, for empiric treatment of patients with suspected line sepsis
- Dialysis catheter-related infection: treat as immunocompromised. Dose accordingly.

ADDITIONAL DIAGNOSTIC AND THERAPEUTIC COMMENTS
- The catheter must be removed and a new catheter inserted in a different location (if still needed)
- If it will be difficult to remove catheter, consult ID
- See Candidemia key messages for Candida CLIs

*Based on TGH, MSH, TWH ICU blood isolates antibiogram (all Gram negatives)
**Based on TGH hospital-wide non-urine isolates antibiogram (all Gram negatives)

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**β-Lactam Allergy**

**COOMBS AND GELL CLASSIFICATION OF HYPERSENSITIVITY REACTIONS**

<table>
<thead>
<tr>
<th>Type</th>
<th>Mediator</th>
<th>Onset</th>
<th>Clinical Reaction</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>IgE antibodies</td>
<td>&lt; 1 hour (rarely 1-72 hours)</td>
<td>Anaphylaxis, urticaria, angioedema, hypotension, bronchospasm, laryngeal edema, pruritus</td>
<td>Anaphylaxis with penicillins: ~0.01-0.05% Anaphylaxis with cephalosporins: ~0.0001-0.1% Patients with anaphylaxis should not be given the offending drug again</td>
</tr>
<tr>
<td>II</td>
<td>IgG and IgM antibodies</td>
<td>&gt; 72 hours</td>
<td>Hemolytic anemia, thrombocytopenia, neutropenia</td>
<td>These reactions are drug specific, so the offending drug should be avoided in the future</td>
</tr>
<tr>
<td>III</td>
<td>IgG and/or IgM complexes</td>
<td>&gt; 72 hours</td>
<td>Serum sickness (fever, cutaneous eruptions, lymphadenopathy, arthralgias, myalgias), Glomerulonephritis Small vessel vasculitis Drug Fever</td>
<td>The antibody-antigen complexes can precipitate in tissues and potentially affect any end organ.</td>
</tr>
<tr>
<td>IV</td>
<td>T-cells</td>
<td>&gt; 72 hours</td>
<td>Contact dermatitis Pustulosis</td>
<td>Incidence is low Eosinophilia, bulous exanthems and immune hepatitis may be due to T-cell activation as well</td>
</tr>
</tbody>
</table>

**IDIOPATHIC REACTIONS**
- Not clearly immune mediated
- Non-pruritic morbilliform and maculopapular rash (which occur in 3-7% of children that take amoxicillin) → if occurs, not a contraindication to taking the antibiotic again
- Stevens-Johnson Syndrome, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and erythema multiforme are rare with beta-lactams but because of the severity, the culprit antibiotic should be avoided

**CROSS-REACTIVITY**
- Between Penicillins and Cephalosporins
  - The widely cited risk of cross-reactivity between penicillins and cephalosporins of 8-10% is based on studies from the 1970s and is now known to be flawed
  - Cross-reactivity between penicillin or amoxicillin and cephalosporins is due to similarities in side chains so there will only be significant risk of cross-reactivity between those with a similar side chain at C-3 or C-7 (see Table below). For example, cefazolin is not expected to cross-react with any penicillin or cephalosporin as it does not have a similar side chain to any other beta-lactam, hence its absence from the table
- Between Cephalosporins
  - Cross-reactivity amongst cephalosporins is low due to the significant heterogeneity of side chains (C-3 and C-7).
  - Therefore, if your patient has a cephalosporin allergy, you can safely prescribe another cephalosporin that has dissimilar side chains (both C-7 and C-3 side chains must be different).
- Between Penicillins and Carbapenems
  - Cross-reactivity is ~1%
Table 1. Groups of cephalosporins and beta-lactams with similar C3 and C7 side chains

<table>
<thead>
<tr>
<th>Similar C-7 side chain. Cross reactions between agents within one group is possible</th>
<th>Similar C-3 side chain. Cross reactions between agents within one group is possible</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong></td>
<td><strong>Group 2</strong></td>
</tr>
<tr>
<td>Penicillin</td>
<td>Amoxicillin</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>Ampicillin</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>Cefaclor</td>
</tr>
<tr>
<td><strong>Group 3</strong></td>
<td><strong>Group 4</strong></td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>Cefotaxime</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td><strong>Group 5</strong></td>
<td><strong>Group 6</strong></td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>Cefixime</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>Ceftazidime</td>
</tr>
</tbody>
</table>

REFERENCE

Empiric Use of Antifungals

**SPECTRA OF ACTIVITY OF ANTIFUNGAL AGENTS (in alphabetical order):**

<table>
<thead>
<tr>
<th>Fungus</th>
<th>Amphotericin B</th>
<th>Fluconazole</th>
<th>Posaconazole</th>
<th>Voriconazole</th>
<th>Echinocandins class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus sp.</td>
<td>+ (± for A. terreus)</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+ (± for C. parapsilosis)</td>
</tr>
<tr>
<td>Candida sp.</td>
<td>+</td>
<td>± (C. krusei is resistant; dose-dependent for C. glabrata)</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Cryptococcus sp.</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

**ANTIFUNGALS REGIMENS AVAILABLE INCLUDE:**

<table>
<thead>
<tr>
<th>Class</th>
<th>Regimens (usual dosing) in alphabetical order by drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azoles</td>
<td>Fluconazole 800 mg IV/PO daily</td>
</tr>
<tr>
<td></td>
<td>Posaconazole† 200 mg PO Q6H for invasive fungal infections</td>
</tr>
<tr>
<td></td>
<td>-200 mg PO TID for prophylaxis in GVHD</td>
</tr>
<tr>
<td></td>
<td>Voriconazole 6 mg/kg IV/PO Q12h x2 doses then 4 mg/kg IV/PO x2 doses for invasive aspergillosis</td>
</tr>
<tr>
<td>Echinocandins</td>
<td>Anidulafungin† 200 mg Day 1 then 100 mg IV daily</td>
</tr>
<tr>
<td></td>
<td>Caspofungin 70 mg IV Day 1 then 50 mg IV daily</td>
</tr>
<tr>
<td>Polynens</td>
<td>Amphotericin B deoxycolate 0.5-1 mg/kg IV daily</td>
</tr>
<tr>
<td></td>
<td>Liposomal amphotericin 3 mg/kg IV daily</td>
</tr>
</tbody>
</table>

†UHN only

For management of documented candidemia, please refer to “ASP Simple Messaging—Candidemia”.

**IN WHOM SHOULD EMPIRIC ANTIFUNGALS BE CONSIDERED?**

- In critically ill patients, risk factors for candidemia are
  - Intra-abdominal sepsis, especially if achievement of source control is uncertain
  - Exposure to broad-spectrum antibiotics
  - Presence of central venous catheter
  - Total parenteral nutrition
  - Renal replacement therapy
  - Exposure to systemic corticosteroid and other cell-mediated immunosuppressive therapy

- In febrile neutropenic patients, particularly in those with fever for longer than 4d despite appropriate empiric antibiotics

**SELECT INDICATIONS OF SPECIFIC ANTIFUNGALS:**

Fluconazole: empiric treatment
- in azole-naïve patients
- in areas where C. albicans accounts for the majority of yeast isolates—MSH ICU and TGH CVICU

Voriconazole: empiric treatment of invasive aspergillosis

Posaconazole:
- alternative to liposomal amphotericin and voriconazole in treatment of invasive aspergillosis
- prophylaxis of invasive fungal infections in bone marrow transplant patients with GVHD

Echinocandins:
- Empiric treatment of candidemia
  - in azole-experienced (e.g. fluconazole prophylaxis) patients
  - in areas where non-albicans yeast account for majority of yeast isolates—TWH ICU and TGH ICU
- caspofungin is an alternative to voriconazole and L-AMB for invasive aspergillosis

Amphotericin B deoxycolate: alternative to azoles or echinocandins for candidemia

Liposomal amphotericin (L-AMB):
- alternative to voriconazole in invasive aspergillosis due to progression of disease
- alternative to amphotericin deoxycolate in those at risk of nephrotoxicity (age>50, concomitant nephrotoxic agents, renal insufficiency at baseline)
- treatment of invasive fungal infections involving the CNS
**ADDITIONAL DIAGNOSTIC AND THERAPEUTIC COMMENTS**

- Serum galactomannan twice weekly in high-risk febrile neutropenic patients as surveillance testing for invasive aspergillosis
- Bronchoscopy ideally within 72h of initiation of empiric antifungal (if not before) to obtain sample for staining and fungal cultures, and to rule out other infections in those with suspected invasive aspergillosis.

**References**


TMP-SMX is an excellent agent for susceptible organisms (e.g. Enterobacter), with high oral bioavailability, high tissue penetration (e.g. CNS, bone, soft tissues, lung) with a relatively low likelihood of C. difficile.

TMP-SMX is an excellent anti-staphylococcal agent, which can be used in staphylococcal skin and soft tissue infections and staphylococcal pneumonia (incl. most MRSA) without accompanying bacteremia.

Because of resistance with Group A streptococci, TMP-SMX should not be used as monotherapy for non-purulent cellulitis.

TMP-SMX has significant safety issues related to renal insufficiency, hyperkalemia and drug interactions in older patients and those with chronic medical conditions (e.g. chronic kidney disease, DM, peripheral vascular disease, etc.), especially when used in settings where patients cannot be carefully monitored (incl. upon discharge). It should therefore be used with close monitoring in the elderly, those requiring prolonged treatment, and/or those with diabetes, renal dysfunction, or haemotological disease.

The risk of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis is extremely low with TMP-SMX (~4.3 cases/million users in one week). However, it is 8-30 times higher than other antimicrobials.

TMP-SMX has significant drug interactions (eg. warfarin, oral hypoglycemic agents)

REFERENCE:

Candidemia (Yeast)

**EMPIRIC CHOICE**
- In non-neutropenic patients: fluconazole 800 mg once daily; if recent azole use or hemodynamically unstable, then an echinocandin
- In neutropenic patients: amphotericin B liposomal 3 mg/kg iv once daily or an echinocandin

**DURATION**
- Repeat blood cultures at 48 hours after first cultures, and then at Day 4 and 7.
- 2 weeks after first negative blood culture + resolution of symptoms attributable to candidemia in absence of metastatic complications

**TOP FIVE ORGANISMS** (what we expect for common organisms)
- C. albicans
- C. glabrata
- C. parapsilosis
- C. tropicalis
- C. krusei

**CURRENT RESISTANCE ISSUES**
- Echinocandin not recommended for *C. parapsilosis* due to higher MICs
- *C. glabrata* should be empirically treated with echinocandin

**IMMUNOCOMPROMISED HOST CONSIDERATION**
- Amphotericin B liposomal 3 mg/kg iv once daily
- Fluconazole if less critically ill and no recent azole exposure
- Duration 2 weeks after resolution of neutropenia and last (+) blood culture and resolution of signs and symptoms of infection
- Febrile patient with hematologic malignancy recovering from neutropenia at risk for hepatosplenic (chronic disseminated) candidiasis (different treatment strategy)
- Transaminitis in the first week of therapy is unlikely due to fluconazole-associated toxicity

**ADDITIONAL DIAGNOSTIC AND THERAPEUTIC COMMENTS**
- ID consultation is strongly recommended (ID is always notified of blood cultures growing Candida)
- Remove all intravascular devices, replace if needed at different site
- Ophthalmology assessment to rule out ophthalmic disease within 1 week of therapy (or after count recovery in neutropenic patient)

**REFERENCES**

Disclaimer: This document is intended for internal use at Mount Sinai Hospital and University Health Network. Recommendations herein are based on existing literature and clinical practice and are subject to change at any time. Please refer to the Terms and Conditions for more details.
**Influenza A and B**

**EMPIRIC CHOICE**
- Treatment (to be started within 48 hours of symptom onset):
  - Standard dose: oseltamivir 75 mg p.o./ng twice daily x 5 days.

**ROUTE**
- p.o./NG/PEG

**DOSE**
- Renal dysfunction (CrCl < 30mL/min) 75 mg daily
- Hemodialysis: 75 mg daily post dialysis on dialysis days
- Children ≥ 12 months: > 40 kg 75 mg/dose p.o. BID
- Obesity: No specific dosage adjustment indicated

**DURATION**
- Treatment: 5 days
- Prophylaxis: Consult ID or Infection Prevention & Control

**ALTERNATIVES FOR ALLERGIES**
- None

**TOP FIVE ORGANISMS**
- Influenza A and B

**CURRENT RESISTANCE ISSUES**
- Consult ID as known or suspected drug resistance should be handled on a case by case basis.
- Intravenous zanamivir (Special Access Program only) is the treatment of choice for patients who develop prolonged acute influenza illness despite appropriate treatment with oseltamivir, or in some cases of documented resistance to oseltamivir.

**IMMUNOCOMPROMISED HOST CONSIDERATION**
- Immunocompromised hosts (e.g., SOT, HSCT, leukemia) need to be regarded as an especially vulnerable group.
- As early signs of influenza may be masked by symptoms associated with underlying disorders or their treatment, treating such patients should done with a high level of suspicion for influenza virus infection and be especially vigilant for the rapid development of oseltamivir resistance.
- Duration of therapy should be determined in conjunction with ID.

**ADDITIONAL DIAGNOSTIC AND THERAPEUTIC COMMENTS**
- If clinical suspicion remains high for a diagnosis of influenza despite a negative NP swab, a bronchoscopy should be performed to obtain a lower respiratory tract sample and empiric therapy with oseltamivir may be continued until this result becomes known. If both NP swab and bronchoscopy specimen results are negative for influenza, it is reasonable to consider stopping oseltamivir therapy.
- There is no clinical or virological advantage with oseltamivir 150mg twice daily compared with standard dose in patients with severe influenza admitted to hospital.

Disclaimer: This document is intended for internal use at Mount Sinai Hospital and University Health Network. Recommendations herein are based on existing literature and clinical practice and are subject to change at any time. Please refer to the Terms and Conditions for more details.
Double vs. Single Coverage in Management of *Pseudomonas aeruginosa* Infections

**EMPIRIC CHOICE:**
Choice of antibiotic regimen should be guided by prior exposure and local susceptibility data.

Antibiotic regimens active against *P. aeruginosa* at MSH and UHN include:

- Piperacillin-tazobactam 4.5 g iv Q6H
- Ceftazidime 2 g iv Q8H
- Meropenem 1g iv Q8H (exception: CNS infection—Consult ID)
- Aminoglycosides: gentamicin or tobramycin 5 mg/kg IV daily; amikacin 15 mg/kg IV daily
- Ciprofloxacin 400 mg iv Q8H or 750 mg p.o. Q12H

**DOUBLE VS. SINGLE COVERAGE**

- In patient care areas where *P. aeruginosa* susceptibility is high, routine double coverage with anti-pseudomonal agents is not warranted.
- Multi-drug resistant (MDR) *P. aeruginosa* is associated with prior antibiotic exposure.
- During critical illness (e.g. septic shock) and in those vulnerable to severe infections due to immunocompromised state, “upfront” double anti-pseudomonal coverage may improve the probability of having at least one active regimen until susceptibility is known. Most commonly studied regimens include an antipseudomonal beta-lactam plus an aminoglycoside.
- MSH-UHN Ventilator-Associated Pneumonia algorithm recommends the addition of an aminoglycoside (gentamicin or tobramycin) to a beta-lactam agent (piperacillin-tazobactam or meropenem) in patients with septic shock.
  
  Link: [http://www.antimicrobialstewardship.com/sites/default/files/msh-uhn_vap_algorithm_0.pdf](http://www.antimicrobialstewardship.com/sites/default/files/msh-uhn_vap_algorithm_0.pdf)
- *High Risk* Febrile Neutropenia Protocol for Malignant Haematology patients recommends gentamicin plus piperacillin-tazobactam combination empirically for up to 72 hrs. Empiric therapy for febrile neutropenic patients should always have activity against *P. aeruginosa*.
  
- Once susceptibility is known for the *P. aeruginosa* isolate, antibiotic therapy should be de-escalated to monotherapy accordingly, and at adequate dosing. Ongoing double coverage has not been supported in clinical trials, and may have been associated with adverse events such as nephrotoxicity.

**CURRENT RESISTANCE ISSUES**

Local *P. aeruginosa* susceptibility data (courtesy of Dr. Sue Poutanen) should be used to determine the most appropriate empiric approach:

<table>
<thead>
<tr>
<th>Specimen source</th>
<th>TG ICU</th>
<th>TW ICU</th>
<th>MSH ICU</th>
<th>PMH (all units*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>Tobramycin: amikacin: ≥80% susceptible</td>
<td>• All regimens: ≥80% susceptible</td>
<td>Piperacillin-tazobactam; tobramycin; amikacin: ≥80%</td>
<td>ALL regimens: ≥80% susceptible EXCEPT ceftazidime (74%)</td>
</tr>
<tr>
<td></td>
<td>Meropenem; piperacillin-tazobactam: 70-79%</td>
<td>• Rest of alternatives: 70-79%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gentamicin; ciprofloxacin: &lt;70%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>No isolates</td>
<td>All regimens: ≥80% susceptible</td>
<td>Piperacillin-tazobactam; amikacin: 100%</td>
<td>All regimens: ≥80% susceptible EXCEPT ceftazidime (75%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rest of alternatives: ≤69%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*To be interpreted with caution as it included all oncology patients and not just those with malignant haematological diseases, who may have higher risk of MDR *P. aeruginosa* due to frequent antibiotic exposure.

§To be interpreted with caution—based on a small number of isolates

**IMMUNOCOMPROMISED HOST CONSIDERATION**

Upfront double coverage may improve the probability of adequate empiric therapy, but once susceptibility is known, antibiotic regimen should be de-escalated to monotherapy accordingly. See also above comments on *High Risk* Febrile Neutropenia Protocol.
REFERENCE:
**S. aureus BACTEREMIA**

**EMPIRIC CHOICE**
- vancomycin 15 mg/kg iv q12h (targeting ~15ug/mL trough)
- cloxacillin 2 g iv q4h if known MSSA or patient known to be MRSA-negative

**DURATION**
- 14 days minimum. The decision to treat for longer is controversial. We currently recommend 28 days unless a TTE is normal OR a TEE is negative for infective endocarditis.

**ALTERNATIVES FOR ALLERGIES**
- vancomycin
- daptomycin (if cannot administer β-lactam and vancomycin)

**CURRENT RESISTANCE ISSUES**
- Approximately 25% of community-acquired isolates of *S. aureus* are methicillin-resistant. MRSA bacteremia is uncommonly acquired in hospitalized patients at MSH and UHN who are known to be MRSA-negative.
- Patients with MRSA bacteremia with a high-vancomycin MIC (≥2 ug/mL) should be referred to ID. They are associated with worse clinical outcomes/higher failure rates than patients with a low MIC. In addition, patients with MSSA with a high-vancomycin MIC are also associated with worse clinical outcomes, even when treated with β-lactams. Additionally, no drug has been shown to be superior to vancomycin for MRSA.

**IMMUNOCOMPROMISED HOST CONSIDERATION**
- None relevant

**ADDITIONAL DIAGNOSTIC AND THERAPEUTIC COMMENTS**
- ID consultation is strongly recommended in most situations (ID is always notified of blood cultures growing *S. aureus*).
- If line-associated, the venous catheter should be removed.
- Repeat blood cultures at 48h to demonstrate sterilization of blood.
- Patients on vancomycin should have Therapeutic Drug Monitoring (TDM) instituted.
- Approximately 20% of catheter-associated SAB is associated with infective endocarditis.
- Daptomycin should be considered if patients are failing vancomycin therapy.
- We do not recommend use of a second agent (e.g. aminoglycoside or rifampin) for SAB

**REFERENCES:**