**Community Acquired Pneumonia - Adult**

**Treatment Regimens**

*Streptococcus pneumoniae* (pneumococcus) is the most serious common cause of pneumonia and empiric therapy must include an antibiotic with predictable activity.

In VIHA, resistance to *S. pneumoniae* isolates have been increasing such that, 23% of *S. pneumoniae* isolates are now resistant to macrolides and 16% are resistant to doxycycline. In contrast 98% of *S. pneumoniae* isolates are sensitive to high dose amoxicillin (1 g TID).

**Prior antibiotic use in the last 3 months** is a significant consideration in empiric therapy selection. Use of an agent from a different class of antibiotic is highly recommended.

<table>
<thead>
<tr>
<th>TREATMENT SETTING</th>
<th>SUGGESTED REGIMEN (7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OUT-PATIENT</strong></td>
<td>amoxicillin 1 g PO TID</td>
</tr>
<tr>
<td></td>
<td>If concerned about comorbidities or atypical pathogens <strong>add:</strong></td>
</tr>
<tr>
<td></td>
<td>doxycycline 100 mg PO BID with food</td>
</tr>
<tr>
<td></td>
<td>or clarithromycin 500 mg PO BID</td>
</tr>
<tr>
<td><strong>NURSING HOME</strong>¹</td>
<td>amoxicillin-clavulanate 500 mg PO TID or 875 mg PO BID</td>
</tr>
<tr>
<td><strong>IN-PATIENT</strong>¹ (Non-ICU)</td>
<td>cefTRIAXone 1 g IV q24h</td>
</tr>
<tr>
<td></td>
<td>If concerned about comorbidities or atypical pathogens <strong>add:</strong></td>
</tr>
<tr>
<td></td>
<td>doxycycline 100 mg PO BID with food</td>
</tr>
<tr>
<td></td>
<td>or clarithromycin 500 mg PO BID²</td>
</tr>
</tbody>
</table>

**Allergy to Penicillins**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (e.g. rash)</td>
<td>cefuroxime axetil 500 mg PO BID</td>
</tr>
<tr>
<td>Severe Penicillin (e.g. anaphylaxis or angioedema) and/or allergy to Cephalosporins</td>
<td>moxifloxacin 400 mg PO daily³</td>
</tr>
</tbody>
</table>

**FOOTNOTES:**

¹ **Suspected/Confirmed Aspiration:** Antimicrobial therapy for the treatment of aspiration without signs and symptoms of infection is usually not indicated. Risk factors for the development of aspiration pneumonia include advanced age, dysphagia, gastric dysmotility, and poor oral hygiene. Gram-negative and gram-positive organisms represent the majority of pathogens, with anaerobes being rarely involved. Specific anti-anaerobic treatment is not routinely warranted but may be indicated in patients with severe periodontal disease, putrid sputum, or evidence of necrotizing pneumonia or lung abscess on chest X-ray.

² or **azithromycin** 500 mg IV daily if unable to take oral therapy.

³ or **moxifloxacin** 400 mg IV daily if unable to take oral therapy.
Community-Acquired Methicillin-Resistant Staphylococcus aureus (CA-MRSA) Skin & Soft Tissue Infections (SSTI): Overview and Management

To address the growing problem of CA-MRSA SSTI within our health authority, the VIHA Antimicrobial Review Subcommittee (VIHA-ARS) of the Pharmacy and Therapeutics Committee has developed a treatment algorithm (see insert) to provide direction in managing these infections and to encourage a consistent treatment approach. This newsletter provides a brief overview of CA-MRSA and key points regarding treatment found in the algorithm.

Background

Methicillin-resistant Staphylococcus aureus (MRSA) has been a prominent pathogen, especially in hospitals and nursing homes, since the 1960s. The first case of MRSA reported in Canada was in 1981.\(^1\) Methicillin-resistant Staphylococcus aureus (MRSA) infections have until relatively recently been mostly nosocomial. The emergence of a new strain of MRSA causing predominantly (but not exclusively) community-acquired infections has changed that, resulting in a distinction between hospital-acquired (HA) and community-acquired (CA) strains.\(^2\) CA-MRSA infections have been observed globally, and were first noted in Canada in an Aboriginal population in Alberta from 1986 to 1989.\(^2\) CA-MRSA has since become an important pathogen implicated particularly in skin and soft tissue infection, but also in more severe disease including sepsis, necrotizing fasciitis, purpura fulminans, toxic shock syndrome, necrotizing pneumonia and empyema.\(^2\)

Genetic Distinction of CA-MRSA

As demonstrated in Figure 1, the nomenclature for the types of MRSA are not necessarily reflective of the source of acquisition. CA-MRSA and HA-MRSA are genetically distinct from each other and as such have different antimicrobial resistance profiles and are associated with different clinical syndromes.\(^3,4\) Both types of MRSA carry the mecA gene complex, which is carried on a specific integrative genetic element known as the staphylococcal cassette chromosome (SCC), and is responsible for beta-lactam resistance.\(^5\) There are five different SCCmec types (I through V); types I, II, and III are found predominantly in HA-MRSA isolates, whereas types IV and V are found in CA-MRSA isolates.\(^5\) This distinction accounts for the wider range of antimicrobials to which CA-MRSA are susceptible.

Infectious Disease

Key Points for Managing CA-MRSA SSTI:

- Systemic antibiotics are often unnecessary for localized disease with no systemic features.
- There are no clinical data to support combination therapy over monotherapy for treating CA-MRSA SSTI. Reserve combination therapy for severe infection.
- Rifampin should never be used on its own due to the potential for rapid development of resistance.
- Vancomycin dosing should be weight-based at 15 mg/kg, administered every 12 hours for patients with normal renal function (target trough before 3rd or 4th dose, 10-15 mg/L).
- If CA-MRSA suspected, always collect specimen(s) for culture and sensitivity.
Table 1 summarizes the typical antimicrobial susceptibilities and associated infections of CA-MRSA and HA-MRSA. In Canada, 10 strains of MRSA have been identified and labeled as CMRSA-1 (Canadian MRSA-1) to CMRSA-10 (Canadian MRSA-10). The dominant circulating strain of CA-MRSA in North America is CMRSA-10, which is equivalent to USA300.²

Table 1. Comparison of associated clinical syndromes and typical antimicrobial susceptibilities of CA-MRSA and HA-MRSA in VIHA

<table>
<thead>
<tr>
<th>Associated clinical syndromes</th>
<th>CA-MRSA</th>
<th>HA-MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and soft tissue infections (furuncles, skin abscesses, cellulitis, folliculitis, impetigo, fasciitis, pyomyositis, wound infections), postinfluenza necrotizing pneumonia</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Nosocomial pneumonia, nosocomial- or catheter-related urinary tract infections, intravascular catheter or bloodstream infections, surgical-site infections</td>
<td>S</td>
<td>R</td>
</tr>
</tbody>
</table>

Typical antimicrobial susceptibilities

- Vancomycin: S
- Linezolid: S
- Rifampin: S
- TMP/SMX: S
- Tetracycline: V
- Clindamycin: R
- Macrolides: R
- Gentamicin: S
- Fluoroquinolones: R

S = susceptible; R = resistant; V = variable; TMP/SMX = trimethoprim/sulfamethoxazole
Virulence Factors

CA-MRSA is distinguished also by the presence of certain virulence factors. Of these, a frequently occurring feature of CA-MRSA is the production of an exotoxin called Panton-Valentine Leukocidin (PVL), which produces tissue necrosis, mediated by cytokine release, and leukopenia (see Figure 2).2, 6 This toxin may account for some of the hallmark presentations of CA-MRSA infections, including furunculosis and necrotizing pneumonia with a propensity to abscess formation.6 Based on this feature of CA-MRSA, it has been suggested that antimicrobial agents with the ability to inhibit exotoxin production (e.g. clindamycin and linezolid) may have an advantage.7 Currently, there is no clinical trial data to confirm or refute this hypothesis.

Risk Factors

Risk factors for CA-MRSA include intravenous drug use, prior antibiotic use, presence of underlying diseases such as diabetes mellitus, malignancy, and chronic skin disease, homelessness/shelter living, incarceration, aboriginal status, and origin from a known area/population with high rates of CA-MRSA.8, 9 Populations in whom CA-MRSA cases have been concentrated include children (particularly those in day care centers), military recruits, incarcerated people, men who have sex with men, sports teams, and native populations.3, 10 Sources of infection in community outbreaks of MRSA infection include close contact as well as shared contaminated objects such as athletic equipment, towels, and benches. It has also been hypothesized that cutaneous MRSA infection may be a sexually transmitted disease.2 It is important to note that CA-MRSA infections have affected a large number of people without the recognizable risk factors listed here.6

Algorithm for the Treatment of CA-MRSA SSTI (see insert)

There are unfortunately few clinical outcome data pointing to the optimal treatment approach for CA-MRSA SSTI leaving many unanswered questions. The algorithm developed by the VIHA-ARS is based on published review literature, a consensus of local expert opinion, as well as local susceptibility patterns of CA-MRSA. Based on the best data that exist, a stepwise approach to the management of typical patients with suspected CA-MRSA SSTI is provided, according to degree of disease severity.

Most patients with mild infection (localized disease with no systemic features) can be managed as outpatients with abscess drainage and/or topical antibiotics alone. Patients with moderate infection (presence of multiple abscesses and/or cellulitis with minimal systemic features) can usually be treated with single agent oral antibiotic therapy. Antibiotic choices include trimethoprim/sulfamethoxazole (TMP/SMX), doxycycline, or clindamycin. If doxycycline or TMP/SMX are chosen, consideration should be given to the addition of a second agent (e.g. cephalexin or penicillin V) for the coverage of Group A streptococcal infection if there is a high index of suspicion that this organism could be contributing to infection (e.g. rapid onset, lymphangitic streaking, regional lymphadenopathy). Some specialists favor routine combination therapy with rifampin in cases where susceptibility has been demonstrated, for a potential synergistic effect against staphylococcal species, although a consensus on this approach has not been established.8, 11 It should be remembered that rifampin is a potent enzyme inducer of numerous cytochrome P450 (CYP450) enzymes, including 2B6, 2C8, 2C19, 2C9, 2D6, 3A4, 3A5, and 3A7, which can result in clinically important drug interactions.12 Also, rifampin should not be used as a single agent as resistance can develop rapidly.11 Because of limited evidence supporting the use combination therapy with rifampin, we recommend that rifampin be reserved for recurrent CA-MRSA infections.
Patients with severe infections usually require parenteral antibiotic therapy with vancomycin in addition to an oral agent active against CA-MRSA (e.g. TMP/SMX, doxycycline, or clindamycin). To ensure adequate concentrations at the site of infection, vancomycin should initially be dosed at 15 mg/kg, administered every 12 hours with normal renal function. Further dose adjustments should be made according to trough concentrations, drawn prior to the third or fourth dose (target 10-15 mg/L). As a protein synthesis inhibitor, clindamycin (administered parenterally) may have a role in decreasing bacterial toxin production and should be considered if the infection is considered life- or limb-threatening and/or the involvement of bacterial toxin production is suspected. The infectious diseases service or other appropriate specialty should be consulted promptly in the event of life- or limb-threatening infection.

The preceding paragraphs briefly describe the main points in the treatment of CA-MRSA SSTI as illustrated in the algorithm. The algorithm should be reviewed in detail for appreciation of the more subtle nuances in treatment approach. Finally, microbial surveillance is of utmost importance in the management of suspected CA-MRSA SSTI and obtaining quality specimens for culture and sensitivity for infections of all degrees of severity is recommended, even if the results are not anticipated to influence treatment decisions.

Written by: Curtis Harder, B.Sc. (Pharm), ACPR, Pharm D
Clinical Pharmacy Specialist – Adult ICU

Reviewed by: VIHA - Antimicrobial Review Subcommittee

References
Algorithm for treatment of CA-MRSA skin & soft tissue infection (SSTI)
Vancouver Island Health Authority

Suspected CA-MRSA SSTI
Decision based on epidemiology, clinical presentation, and risk factors (see reverse)

MILD
- Localized disease with no systemic features
- May include infected scratches, insect bites, furuncles, small abscesses, impetigo, or folliculitis
- Cellulitis NOT present

MANAGE AS OUTPATIENT
1. Drain abscess if present.
2. Culture fluid from abscess or purulent lesion.
3. If impetigo or folliculitis consider course of TOPICAL antibiotic (e.g. mupirocin 2% or fusidic acid 2%).
4. Systemic antibiotics are generally NOT required.

Await susceptibility results (48-72 hrs)

MRSA
- Is isolate susceptible to current antibiotic?
  YES
    Continue original antibiotic regimen.
  NO
    Adjust antibiotics according to susceptibility results.

MSSA
- Change antibiotic(s) to a single PO agent optimally effective against MSSA (Table 3).

Clinical deterioration at 72 hours?
- NO
  Continue with single agent
- YES
  Reassess for presence of bacterial reservoir (e.g. tenosynovitis, bursitis, abscess). Consider imaging studies, drainage procedure, and/or adding second PO agent (Table 1).

Clinical improvement at 7 days?
- YES
  Consult infectious diseases or other appropriate specialty and/or re-assess for presence of bacterial reservoir (e.g. tenosynovitis, bursitis, abscess). Consider imaging studies, drainage procedure, and/or adding second PO agent (if not already added; Table 1).
  Consider discontinuing treatment or continuing for no more than 7 days
- NO
  Consult infectious diseases or other appropriate specialty and reassess for presence of bacterial reservoir (e.g. tenosynovitis, bursitis, abscess). Consider imaging studies, drainage procedure, and/or adding second PO agent (Table 1).

Clinical deterioration or no improvement at 72 hours?
- NO
  Continue full treatment course (7-14 days). Stepdown to PO treatment when appropriate (see stepdown criteria on reverse).
- YES
  Consult infectious diseases or other appropriate specialty

SEVERE
- Extensive cellulitis and/or large or multiple abscesses
- Significant associated systemic features

MANAGE AS INPATIENT
1. Drain abscess if present.
2. Culture fluid from abscess or purulent lesion.
3. Begin course of single empiric IV antibiotic(s) (Table 2). If systemic features present, may require initial outpatient IV antibiotic (Table 2). Where facilities exist, consider referral to OPAT clinic with first dose of single IV antibiotic given in ED.
4. For life- or limb-threatening infections, consult infectious diseases or other appropriate specialty immediately.

Await susceptibility results (48-72 hrs)

MRSA
- Clinical deterioration or no improvement at 72 hours?
  NO
    Continue MRSA coverage (Severe: IV vancomycin + PO agent effective against CA-MRSA +/- IV clindamycin)
  YES
    Consult infectious diseases or other appropriate specialty

MSSA
- Change antibiotic(s) to a single IV agent optimally effective against MSSA (Table 3). Stepdown to PO treatment when appropriate (see stepdown criteria on reverse).

ABBREVIATIONS
CA = community acquired
ED = Emergency Department
MRSA = methicillin-resistant Staphylococcus aureus
MSSA = methicillin-sensitive Staphylococcus aureus
OPAT = outpatient antimicrobial therapy
Algorithm for treatment of CA-MRSA skin & soft tissue infection (SSTI)
Vancouver Island Health Authority

**NOTE:** This algorithm is to be used as a guide for decision-making with respect to the treatment of presumed CA-MRSA skin and soft tissue infections only. An appropriate treatment pathway for other types of CA-MRSA infections is beyond the scope of this algorithm.

**TABLE 1. EMPIRIC ORAL OPTIONS FOR CA-MRSA**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage</th>
<th>Adult</th>
<th>Pediatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMP-SMX</td>
<td>1-2 DS tabs PO BID</td>
<td>8-12 mg/kg/day (based on TMP component) PO divided BID</td>
<td></td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg PO BID</td>
<td>&gt;8 years: 100 mg PO BID ≤8 years: avoid</td>
<td></td>
</tr>
<tr>
<td>Clindamycin*</td>
<td>450-600 mg PO TID</td>
<td>30 mg/kg/day PO divided TID or QID</td>
<td></td>
</tr>
</tbody>
</table>

**IF RECURRENT CA-MRSA infection consider adding**

- Rifampin 600 mg PO daily or 300 mg PO BID 10-20 mg/kg/day PO given BID

**If Group A streptococcal (GAS) infection suspected (e.g. rapid onset, lymphangitic streaking, regional lymphadenopathy) and patient NOT already receiving clindamycin, consider adding GAS-effective agent**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalexin</td>
<td>500 mg PO QID 40 mg/kg/day PO given QID</td>
</tr>
<tr>
<td>Penicillin VK</td>
<td>300 mg PO QID 40 mg/kg/day PO given TID-QID</td>
</tr>
<tr>
<td>Penicillin allergy</td>
<td>See above</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>See above</td>
</tr>
</tbody>
</table>

*Approximately 30% of CA-MRSA strains in VIHA are non-susceptible to clindamycin. Clindamycin should NOT to be used as single empiric coverage for moderately severe infections.

**TABLE 2. EMPIRIC PARENTERAL OPTIONS FOR CA-MRSA**

Parenteral agent to be used in combination with a single PO agent (Table 1) for treatment of moderate/severe infections associated with systemic features.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>15 mg/kg IV q12h (assuming normal renal function) Target trough levels of 10-15 mg/L</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>600-900 mg IV q8h 30-40 mg/kg/day IV divided q6-8h</td>
</tr>
</tbody>
</table>

Consider adding agent that inhibits protein synthesis for life-and/or limb-threatening infections including necrotizing fasciitis, pyomyositis, septic shock, and Staphylococcal toxic shock syndrome

- Clindamycin

**TABLE 3. PARENTERAL AND ORAL OPTIONS FOR MSSA**

<table>
<thead>
<tr>
<th>Agent</th>
<th>PO Dosage</th>
<th>IV Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cloxacin</td>
<td>500 mg PO QID</td>
<td>40-50 mg/kg/day PO divided QID</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>N/A</td>
<td>1-2 g IV q6h</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>N/A</td>
<td>75 mg/kg/day IV divided q8h</td>
</tr>
<tr>
<td>Clindamycin*</td>
<td>450-600 mg PO TID</td>
<td>10-30 mg/kg/day PO divided TID-QID</td>
</tr>
</tbody>
</table>

* Treatment preference should favor cloxacin or cefazolin, which are bactericidal, over clindamycin, which is bacteriostatic.

**IV to PO stepdown criteria** (all of the following must be met for stepdown):

- Temperature <38°C x 24 hours
- WBC <11 or decreasing trend
- Clinical improvement observed while on IV treatment
- Absence of gastrointestinal abnormalities that may interfere with absorption

**NOTES**

1. There are currently no clinical outcome data to guide preferential selection of initial antimicrobial agent.
2. Typical duration of therapy is 7-10 days but individual clinical circumstances must dictate final decision on duration.
3. Because of the potential for rapid development of resistance, fluoroquinolones should NOT be routinely used even if bacterial isolates show susceptibility.
4. Rifampin should NOT be used as monotherapy due to rapid development of resistance when used as sole antimicrobial.

**Usual features of SSTI suggestive of CA-MRSA**

The index of suspicion for CA-MRSA SSTI should be increased when a patient has ≥1 known epidemiologic risk factors and a consistent clinical presentation with CA-MRSA infection.

1. Risk factors for CA-MRSA infection
   - Intravenous drug use
   - Homelessness/incarceration
   - Aboriginal descent
   - Participation in close contact sports
   - Known close contact with individuals at higher risk
   - History of MRSA infection/colonization
   - Known close contact with someone with history of MRSA infection/colonization
   - Children <2 years
   - Men who have sex with men
2. Characteristic clinical presentation
   - Folliculitis, furuncles/carbuncles, abscesses, and/or cellulitis
   - Simultaneous presence of two or more pustules, often at unrelated sites
   - Pustules are often painful and may or may not be associated with cellulitis

**IV to PO stepdown criteria** (all of the following must be met for stepdown):

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- WBC <11 or decreasing trend
- Clinical improvement observed while on IV treatment
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Infectious Disease Update: March 2011

Appropriate Management of Urinary Tract Infection and Asymptomatic Bacteriuria

Published by the VIHA Antimicrobial Review Subcommittee of the Pharmacy & Therapeutics Committee

Overview

Symptomatic urinary tract infection (UTI) is one of the most common infections encountered in practice requiring antimicrobial treatment. Asymptomatic bacteriuria is also a common problem, variable in prevalence according to certain characteristics like age, sex and presence of genitourinary abnormalities, but is more nuanced in its specific requirement for antimicrobial treatment. The VIHA Antimicrobial Review Subcommittee (VIHA-ARS) has developed treatment algorithms (see insert) to provide direction for the empiric treatment of suspected urinary tract infection and asymptomatic bacteriuria. Because many published guidelines/recommendations recommend empiric antimicrobial agents that are associated with significant resistance, we have endeavored to incorporate local susceptibility data to ensure the best chance of clinical success and to preserve key agents in our antimicrobial armamentarium. These algorithms address the treatment of cystitis, pyelonephritis, and asymptomatic bacteriuria, with a focus on the management of patients seen in or admitted to the hospital.

Uncomplicated Cystitis

Uncomplicated cystitis occurs in young healthy women (average age 16-35 years), and is classically associated with symptoms of dysuria, urinary frequency with or without urgency, and hematuria. Escherichia coli. continues to be the most common pathogen, contributing to approximately 80-85% of infections. Other pathogens are Staphylococcus saprophyticus (~5-15%), Proteus mirabilis, Klebsiella species and occasionally Enterococcus spp. When cystitis is suspected, a midstream urine specimen should be collected for routine and microscopic urinalysis, as well as culture and sensitivity.

Empiric antimicrobial therapy targeting the most likely urinary tract pathogens should be initiated when urinalysis results and symptomatology support the diagnosis of cystitis, even when urine culture and sensitivity results are pending. Urine culture and sensitivity results serve both to establish definitive antimicrobial therapy as well as to provide surveillance data on antimicrobial resistance.

Trimethoprim/sulfamethoxazole (TMP/SMX) and ciprofloxacin have historically been recommended as empiric agents for the treatment of uncomplicated UTI. According to the 2005 VIHA antibiogram, E. coli susceptibilities to TMP/SMX and ciprofloxacin were 79% and 71%, respectively. Current interim data for 2008 indicate susceptibilities of 81% and 77%. By convention, an antimicrobial agent’s efficacy is considered adequate when a target organism’s in vitro susceptibility is greater than 80%. Accordingly, the empiric use of ciprofloxacin as a first-line agent for UTI can no longer be recommended. Resistance to TMP/SMX is also a concern although it remains an alternative in cases of contraindications to other effective therapies.

Uncomplicated cystitis can almost always be treated with orally administered antimicrobials. Based on local susceptibility data, nitrofurantoin, TMP/SMX and cefixime are all reasonable options for empiric treatment. The advantage of TMP/SMX and cefixime is that either can be used effectively for durations as short as 3 days. Nitrofurantoin, given as the macrocrystal formulation for 5 days, has recently been shown to be as effective as 3 days of TMP/SMX. Despite being a relatively old agent, nitrofurantoin has been associated with little bacterial resistance. Selection should take into account previous antimicrobial use, presence of relative/absolute contraindications (e.g. beta-lactam or sulfa allergy, renal impairment), and cost.
Complicated Cystitis

Complicated urinary tract infection occurs in both women and men and in any age group, and is usually characterized by presence of a structural or functional abnormality of the genitourinary tract. In broad terms, complicated cystitis usually occurs in those patients other than young, healthy, non-pregnant women. Complicated infections may include the following features:

- symptoms lasting greater than seven days
- male gender
- females greater than 55 years of age
- diabetes mellitus
- abnormality of the urinary tract, spinal cord injury or multiple sclerosis
- pregnancy
- chronic catheterization
- recurrent UTI

The commonly implicated pathogens include not only those seen in uncomplicated UTI, but also other Enterobacteriaceae, Enterococcus spp, Group B Streptococcus, Pseudomonas aeruginosa and Candida spp. An increasing problem with complicated infections is the emergence of extended spectrum beta-lactamase (ESBL) producing bacteria. Patients who have chronic infections, or who have been recently/recurrently hospitalized are at risk for developing antibiotic resistant organisms, and may require agents beyond the scope of this algorithm.

Generally, treatment for complicated cystitis is indicated for 7 days. In the case of abnormality of the urinary tract (anatomic, functional, or metabolic), treatment is indicated for 10-14 days and often is due to a broader range of possible pathogens, including Enterococcus spp. It is important to note that amoxicillin-clavulanic acid is one of few oral alternatives that provides enterococcal coverage with the exception of E. faecium.

Catheterized Patients

In the chronically catheterized patient with a symptomatic UTI, the catheter should be changed prior to obtaining a urine specimen (through the clean catheter), as indwelling catheters are often colonized with bacteria. In some situations, catheter change alone will improve symptoms, and antibiotics may not be required. Although symptomatic UTI is often accompanied by pyuria identified by routine and/or microscopic urinalysis, pyuria is also present in most patients with indwelling catheters and asymptomatic bacteriuria and thus is not diagnostic of UTI.

Cystitis in Males

First-episode cystitis is usually treated for 7 days. Recurrent cystitis is treated for 6 weeks in conjunction with urologic work-up to rule out chronic bacterial prostatitis.

Diabetes Mellitus

Patients with diabetes are predisposed to infection with group B Streptococci, therefore a beta lactam antibiotic may be preferred.

Recurrent or Relapsing Cystitis

More than 90% of cases of recurrent cystitis 2-4 weeks following treatment are due to reinfection, usually with a different organism or strain. Relapse (with the same organism and strain) is usually within 2 weeks following treatment. However, the urine should be re-cultured in either scenario as there may be a new organism or the sensitivities could have changed from the previous microbiology report.

Pyelonephritis

Pyelonephritis involves the upper urinary tract and is generally associated with systemic symptoms such as fever, chills, nausea, malaise, ipsilateral costovertebral angle tenderness and abdominal or flank pain. Complicating factors for pyelonephritis are similar to those seen with cystitis, and the key differences in approach are reflected in the level of diagnostics and aggressiveness of treatment.

Blood cultures (2 sets), in addition to urine cultures, should be collected to assist in establishing a diagnosis. In the patient who is hemodynamically stable and is able to take medication by mouth, outpatient oral antibiotic treatment may be appropriate. Otherwise, intravenous antibiotics are usually indicated and can be administered through an outpatient antibiotic therapy program (if available) or will require hospital admission. As the patient improves and microbiological susceptibilities become known, antibiotic therapy should be narrowed and/or administered orally to complete a usual treatment course of 10-14 days.

Specific IV to PO switch criteria include:

- temperature less than 38°C for 24 hours
- WBC less than 11 or decreasing trend
- clinical improvement while on IV treatment
Table 1. VIHA susceptibilities of common organisms in UTI (2008)

<table>
<thead>
<tr>
<th>Organism</th>
<th>ampicillin</th>
<th>cephalaxin</th>
<th>amoxicillin/clavulanate</th>
<th>cefixime</th>
<th>ceftriaxone</th>
<th>ciprofloxacin</th>
<th>gentamicin</th>
<th>nitrofurantoin</th>
<th>trimethoprim/sulfamethoxazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli</td>
<td>62%</td>
<td>61%</td>
<td>84%</td>
<td>91%</td>
<td>92</td>
<td>77%</td>
<td>94%</td>
<td>96%</td>
<td>81%</td>
</tr>
<tr>
<td>Staphylococcus saprophyticus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Susceptibility testing is not routinely performed as antibiogram is predictable. Antibiotics of choice are nitrofurantoin, trimethoprim-sulfamethoxazole or ciprofloxacin.</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>95%</td>
<td>N/A</td>
<td>95%</td>
<td>N/A</td>
<td>N/A</td>
<td>62%</td>
<td>N/A</td>
<td>92%</td>
<td>N/A</td>
</tr>
<tr>
<td>Klebsiella pneumonae/oxytoca</td>
<td>0%</td>
<td>88%</td>
<td>92%</td>
<td>94%</td>
<td>94%</td>
<td>97%</td>
<td>98%</td>
<td>45%</td>
<td>94%</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>83%</td>
<td>90%</td>
<td>92%</td>
<td>95%</td>
<td>95%</td>
<td>91%</td>
<td>93%</td>
<td>0%</td>
<td>90%</td>
</tr>
</tbody>
</table>

N/A = not appropriate for this organisms

Table 2. Daily costs* of common oral antibiotic regimens for treating UTI

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Average Daily Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>amoxicillin 500 mg TID</td>
<td>$1.10</td>
</tr>
<tr>
<td>amoxicillin/clavulanic Acid 500 mg TID</td>
<td>$3.00</td>
</tr>
<tr>
<td>cefixime 400 mg once daily</td>
<td>$3.70</td>
</tr>
<tr>
<td>cephalexin 500 mg QID</td>
<td>$1.80</td>
</tr>
<tr>
<td>ciprofloxacin 500 mg BID</td>
<td>$3.40</td>
</tr>
<tr>
<td>nitrofurantoin (Macrobid&lt;sup&gt;®&lt;/sup&gt;) 100 mg BID</td>
<td>$1.48</td>
</tr>
<tr>
<td>trimethoprim/sulfamethoxazole 1 DS tablet BID</td>
<td>$0.26</td>
</tr>
</tbody>
</table>

* Figures listed represent drug acquisition cost only and do not include dispensing fee.
absence of gastrointestinal abnormalities that may reduce absorption.

Like uncomplicated cystitis, uncomplicated pyelonephritis is usually caused by E. coli, although the disease-causing strains have unique virulence characteristics. In complicated pyelonephritis, pathogens include other Enterobacteriaceae (e.g. Enterobacter, Serratia, Proteus, Klebsiella) in addition to E. coli, Pseudomonas, Enterococcus and group B Streptococci. As for complicated cystitis, patients with complicated pyelonephritis who have been recently/recurrently hospitalized are at risk for developing antibiotic resistant organisms, and may require agents beyond the scope of this algorithm. The increased risk of enterococcal involvement in the setting of complicated pyelonephritis generally warrants specific empiric enterococcal treatment with either intravenous ampicillin (in combination with gentamicin or ceftriaxone) or oral amoxicillin/clavulanate.

Gentamicin is a good empiric option for pyelonephritis as it concentrates well in the urine and is highly effective against E. coli. Its pharmacodynamic activity allows it to be given as a once-daily dose for patients with adequate renal function (GFR greater than 60mL/min). Due to the risk of nephrotoxicity and irreversible vestibular and oto toxicity, it is important that gentamicin be switched to an appropriate oral agent as soon as possible.

Asymptomatic Bacteriuria

With the exception of patients who are pregnant or who will be undergoing a urologic procedure where mucosal bleeding is anticipated (e.g. transurethral resection of the prostate), antimicrobial treatment for asymptomatic bacteriuria is generally not indicated. Asymptomatic bacteriuria, while infrequent in adults, may be present in up to 50% of elderly patients, especially females. This increase in bacteriuria is partially attributable to urinary incontinence and catheterization. In this population, routine screening measures are not indicated, as treatment is unwarranted. There is no evidence that asymptomatic bacteriuria in the elderly is associated with incontinence, decreased renal function, or hypertension. Unnecessary treatment leads to increased local resistance to antibiotics and has not been shown to alter overall cognition, morbidity or mortality.

Pregnancy

In pregnancy, asymptomatic patients should be treated as there is an increased risk for pyelonephritis, preterm labor, fetal mortality, and gestational hypertension. Screening for bacteria is recommended at 12-16 weeks. If bacteria are present, pre and post treatment urine cultures are recommended along with monthly urine cultures for the remainder of the pregnancy. Antibiotic treatment is directed toward the specific pathogen cultured in pregnant women with asymptomatic bacteriuria and should be decided on according to urine culture and sensitivity reports. Nitrofurantoin should be avoided near term (36-42 weeks) and during labour, due to the risk of hemolytic anemia in the newborn. Trimethoprim and TMP/SMX should be avoided during the first trimester because of concerns that that trimethoprim may act as a folate acid antagonist and lead to fetal abnormalities. TMP/SMX should also be avoided during the last 6 weeks of pregnancy due to the risk of hemolytic anemia, jaundice and kernicterus in the newborn. Amoxicillin, cephalaxin, and cefixime represent safe options that can be given for the full duration of pregnancy.

Transurethral Resection of Prostate (TURP) or other Urologic Surgery

Empiric antibiotic prophylaxis is often indicated prior to urologic procedures, depending on risk of resultant bacteremia. Urine cultures are collected before high-risk procedure and when positive, antibiotic prophylaxis should be directed toward the specific pathogens cultured.

References

Available upon request.

Written by Laura Lammers, Clinical Pharmacist, and Dr. Curtis K Harder, Clinical Pharmacy Specialist
Overview

To address the continuing problem of *Clostridium difficile* infection (CDI) within our health authority, the VIHA Antimicrobial Review Subcommittee (VIHA-ARS) of the Pharmacy and Therapeutics Committee has developed a treatment algorithm (see below) to provide direction in managing these infections.

Background

After treatment with antibiotics, many patients develop gastrointestinal symptoms ranging from mild diarrhea to severe bloody diarrhea with fever and abdominal pain. Many cases of the milder forms of gastrointestinal illness and most of the severe forms are caused by CDI.

*C. difficile* is a gram positive, anaerobic, spore-forming bacillus that is resistant to most antibiotics. When a person takes an antibiotic, the normal colonic flora are reduced giving *C. difficile*, if present, the opportunity to proliferate. If it lacks the gene for toxin production then disease does not develop. However, if it produces cytotoxin A and/or B, it may cause colitis. *C. difficile* does not invade the colonic mucosa and it only has the potential to cause disease if toxin is produced. Even when toxin is produced, some people become carriers or develop mild self-limited diarrhea while others develop severe colitis and may have multiple relapses.

The clinical course appears to depend on the host immune response to toxin. While most colonized patients won't develop CDI, they represent a large reservoir of *C. difficile* with the potential to contaminate the environment. The spores survive desiccation for months and are resistant to conventional disinfectants. Poor hand hygiene and suboptimal cleaning practices can then easily result in transmission to susceptible patients.

Virulence Factors

*C. difficile* may produce up to six different types of toxins but the main virulence factors are toxin A (tcdA) and toxin B (tcdB). Usually, *C. difficile* isolates from patients with CDI produce both toxin A and B, but variants A+B- and A-B+ have also been found in symptomatic patients.

The “Quebec strain” of *C. difficile* (BI/NAP-1/027) is particularly virulent and is now also widespread in British Columbia. The strain has a dysfunctional tcdC gene inactivating the down regulation of tcdA and tcdB. These strains produce 16 times more toxin A and 23 times more toxin B than other *C. difficile* strains. Another novel characteristic of this strain is that it is resistant to fluoroquinolones. There is concern that increasing fluoroquinolone use is associated with increasing CDI.
Risk Factors

Risk factors for CDI are generally divided into three main groups:

1. **Host factors**: age greater than 65 years; female sex; multiple comorbidities; immune compromised;
2. **Disruption of normal intestinal microflora**: antibiotic exposure within 3 months; medications affecting intestinal tract; loss of intestinal function (ileus, obstruction); chemotherapy; antacids/proton pump inhibitors; procedures (surgery, nasogastric tube, enemas);
3. **Increased exposure to *C. difficile***: admission to hospital; admission to Long Term Care (LTC) facility; poor hand hygiene; infected hospital roommate; prior CDI episodes.

Lab Diagnosis

Patients with suspected CDI should have a stool sample submitted. Formed stool is not appropriate and if submitted will be rejected. The specimen must be liquid enough to move in the container when the container is tilted (Bristol stool chart #7). In VIHA, the sample is first tested using a rapid membrane enzyme immunoassay for the detection of *C. difficile* antigen and toxins A and B. The antigen test detects glutamate dehydrogenase as a screen for the presence of *C. difficile*. If the test is negative, no further testing is necessary. In a recent comparison with nucleic acid amplification test (NAT) methods, the negative predictive value of the antigen test was 99%. The turn around time (TAT) for the initial rapid screen test is less than 24 hours and STAT tests can be arranged following consultation with the medical microbiologist on call. All toxin positive tests are notified to the ward for inpatients and to the physician’s office for outpatients.

If the antigen test is positive but the initial toxin screen test is negative then the patient maybe colonized with a non toxin producing strain of *C. difficile* or the toxin production may be below the detection threshold of the initial toxin screen test. In VIHA, to increase the sensitivity for detection of CDI, a supplemental nucleic acid amplification test (NAT) is performed on all samples when the antigen test is positive and the initial rapid toxin A and B screen is negative. The NAT detects the presence of the toxin B gene, not the presence of free toxin in the stool. Clinical correlation is required to determine if the patient’s illness still meets the case definition when positive NAT results are reported.

Treatment

**Initial episode**
- Mild-to-moderate infection:
  - Metronidazole 500 mg orally 3 times daily (or 250 mg orally 4 times daily) for 10 to 14 days
- Severe infection or unresponsiveness to or intolerance of metronidazole:
  - Vancomycin 125 mg orally 4 times daily for 10 to 14 days

**First recurrence†**
- Mild-to-moderate infection:
  - Metronidazole 500 mg orally 3 times daily for 10 to 14 days
- Severe infection or unresponsiveness to or intolerance of metronidazole:
  - Vancomycin 125 mg orally 4 times daily for 10 to 14 days

**Second recurrence†**
- Vancomycin 125 mg orally 4 times daily for 14 days
- If patient has previously received vancomycin proceed to tapering therapy described below
**Clostridium difficile Infection (CDI)**

**TREATMENT SECTION CONTINUED…**

**Third / subsequent recurrence(s)†**

Vancomycin in tapered and pulsed doses:
- 125 mg orally 4 times daily for 14 days
- 125 mg orally 2 times daily for 7 days
- 125 mg orally once daily for 7 days
- 125 mg orally once every 2 days for 14 days

† A probiotic such as *Saccharomyces boulardii* (Florastor) 500 mg orally 2 times daily for at least 4 weeks maybe added as adjunctive therapy in recurrent CDI. However, the efficacy of probiotics in preventing recurrent *C. difficile* infection is not established because of inconsistent study results. Probiotics are generally safe but should NOT be prescribed to immunocompromised patients, to patients in critical care settings, to patients with central lines in place nor to patients with bloody diarrhea or severe abdominal pain. There have been reports of bacteremia and fungemia associated with probiotics in such settings.

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**Frequently Asked Questions**

1. **What are the main clinical symptoms of Clostridium difficile infection (CDI)?**
   
   Clinical symptoms include: watery or loose stools (ie. more than three times/day); fever; nausea; abdominal pain or cramping.

2. **Aside from antibiotic exposure what other factors put patients at increased risk for CDI?**
   
   The risk for disease increases with: increasing age, severity of underlying diseases, degree of immunocompromise, abdominal surgery or gastrointestinal procedures, presence of a nasogastric tube, anti-ulcer medications (eg. proton pump inhibitors), duration of hospital stay or living in a long term care facility or prior history of CDI.

3. **How is CDI usually treated?**
   
   Initial therapy should, if possible, include discontinuing the inciting antibiotic regimen. CDI will resolve spontaneously in about 20% of patients within 2-3 days of discontinuing the offending antibiotic(s) but most patients require specific antibiotic therapy with po metronidazole or vancomycin for at least 10 days. After treatment, repeat Clostridium difficile testing is NOT recommended if the patients' symptoms have resolved, as patients may remain colonized.

4. **Do asymptomatic patients with a positive Clostridium difficile toxin test result require treatment?**
   
   No, patients without symptoms do NOT require treatment.

5. **Which antibiotic is preferred in the treatment of mild to moderate CDI?**
   
   Metronidazole and vancomycin show similar efficacy in patients with mild infection. Due to the risk of emergence of VRE associated with excess vancomycin usage, **metronidazole remains the preferred agent in patients with mild-to-moderate infection**. Vancomycin may be considered as first line therapy in patients who are greater than 75 years old, have comorbidities or who are immunosuppressed. (Incidentally, a 14 day course of metronidazole 500 mg PO TID costs approximately $4.00 versus a 14 day course of vancomycin 125 mg PO QID which costs approximately $400.00.)
**Clostridium difficile Infection (CDI)**

6. **How long should patients with CDI be treated?**

   In order to reduce the likelihood of recurrence it is important that patients with CDI complete at least 10 days of therapy.

7. **What antibiotic is preferred in the treatment of severe CDI?**

   Vancomycin is recommended as first line therapy in patients with severe infection because of quicker symptom resolution and lower risk of treatment failure.

8. **How do you decide if the CDI is severe?**

   Determination of disease severity is based on clinical judgement and may include any or all of: a marked peripheral leukocytosis; renal dysfunction; severe abdominal pain; fever; hypotension; ileus; or toxic megacolon.

9. **In severely ill patients with CDI should any additional antibiotic therapy be considered along with the po vancomycin?**

   Severely ill patients with ileus may have markedly delayed passage of oral antibiotics from the stomach to the colon. These individuals may benefit from the addition of intravenous metronidazole at a dose of 500 mg every eight hours. Vancomycin therapy per rectum may also be considered although the safety and efficacy of this practice has not been established. Vancomycin 500 mg retention enemas may be given every 4 to 8 hours.

10. **Is there any benefit to combining po metronidazole with po vancomycin in more severe infections?**

    No, there is no evidence that adding po metronidazole to po vancomycin improves outcomes.

11. **When should surgery be considered?**

    Surgery should be considered in patients with severe CDI who fail to improve with medical therapy or if toxic megacolon or colonic perforation is suspected. Toxic megacolon should be considered if the patient develops abdominal distention with diminution of diarrhea; this may reflect paralytic ileus resulting from loss of colonic muscular tone.

12. **What other conditions may resemble CDI?**

    The differential diagnosis for CDI includes: benign or simple antibiotic-associated diarrhea; acute and chronic diarrhea caused by other enteric pathogens; adverse drug reactions (other than antibiotics); ischemic colitis; idiopathic inflammatory bowel diseases; and intra-abdominal sepsis.

13. **Is there any role for antimotility agents in the treatment of CDI?**

    These agents should be avoided. There is little evidence that such agents lead to symptomatic improvement and several anecdotes and case series have associated their use with the development of toxic megacolon in patients with CDI.

14. **Is there any role for cholestryramine in the treatment of CDI?**

    This agent should also be avoided as it is of no proven benefit and may theoretically bind and reduce the activity of the antibiotic therapy.
**Clostridium difficile** Infection (CDI)

15. What is the role of probiotics in the management of CDI?

A probiotic such as *Saccharomyces boulardii* (Florastor) 500 mg orally 2 times daily for at least 4 weeks maybe added as adjunctive therapy in recurrent CDI. However, the efficacy of probiotics in preventing recurrent CDI is not established because of inconsistent study results. Probiotics are generally safe but **should NOT be prescribed to immunocompromised patients, to patients in critical care settings, to patients with central lines in place nor to patients with bloody diarrhea or severe abdominal pain.** There have been reports of bacteremia and fungemia associated with probiotics in such settings.

16. Where can I find more information?

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**Prevention: The Most Important Strategy**

Given the significant morbidity and mortality associated with CDI it is critical that appropriate measures be undertaken to prevent infection and transmission. A multifaceted approach of prudent antimicrobial use along with stringent infection control including hand hygiene, early institution of contact precautions and disinfection of rooms with a sporocidal agent are all essential in preventing CDI and controlling its spread.

**Summary**

Increasing incidence and several recent outbreaks of CDI at VIHA facilities highlight the importance of early diagnosis, prompt institution of stringent infection control practices, and rational antibiotic therapy. New guidelines favour oral metronidazole as the preferred therapy for mild to moderate disease and oral vancomycin as the preferred therapy for those with severe disease or risk factors. The hypervirulent “Quebec strain” of *C. difficile* is widely present in VIHA and British Columbia and is associated with more severe disease and death. It is incumbent on all health care workers to adhere to optimal infection control and on all prescribers to practice good antimicrobial stewardship so as to prevent CDI and limit its transmission.

**References and Further Reading**

Clostridium difficile Infection (CDI)

Written by:
Dr. John Galbraith
Medical Microbiologist, Laboratory Medicine

Reviewed by:
VIHA-ARS
September 2009
Updated January 2012

Clostridium difficile bacteria image on first page from: Science Photo Library Available from URL:
GASTROINTESTINAL

DEFINITIONS USED FOR RISK STRATIFICATION TO GUIDE THERAPY

The following definitions were extracted from the Canadian practice guidelines for surgical intra-abdominal infections. The guidelines are endorsed by the Association of Medical Microbiology and Infectious Disease (AMMI) Canada and the Canadian Association of General Surgeons (CAGS) Committee on Acute Care Surgery and Critical Care.


Community-Acquired

- Involve conditions such as gastroduodenal perforation, ascending cholangitis, cholecystitis, appendicitis or diverticulitis with or without perforation, and pancreatitis without previous surgical intervention or hospitalization.

Healthcare-Associated

- An infectious process that is absent at the time of hospital admission, but becomes evident at 48 hours or more after admission, and includes anastomotic leaks and perforations as well as abscesses that develop as complications of surgery.
- Also includes infections acquired during the course of receiving treatment for other conditions in a health-care setting, including the nursing home, dialysis unit or surgical daycare, within the previous 12 months.

SEVERITY

Categorize by clinical impression:

- Mild to moderate severity (e.g. APACHE II scores less than 15).
- High severity (e.g. APACHE II score equal to or greater than 15).

RISK

Identify high-risk patients for poor outcome by following criteria:

- Community-acquired versus healthcare-associated (see above).
- Previous antibiotic exposure (previous 90 days).
- Underlying co-morbid conditions such as diabetes, severe cardiopulmonary disease or immunosuppression.
Gastroenteritis (Acute)

- Avoid antimotility agents until you have ruled out C. difficile or E. coli 0157:H7 as the cause.
- Do not use bismuth subsalicylate with quinolones as binding decreases quinolone absorption.

**MILD-MODERATE**

**Antibiotic therapy is NOT recommended** unless symptoms severe or prolonged.

**SEVERE**

**Severity criteria (one or more):**

- Defined as including one or more of the following criteria (± fever):
  - approximately 6 or more diarrheal episodes per day
  - bloody diarrhea
  - persistent diarrhea (greater than 3 days)

- If patient has a sepsis presentation, treat as sepsis with a GI source. Refer to early goal directed therapy protocol (not currently provided in these guidelines).
- Culture and C. difficile toxin recommended.
- C. difficile can be a community-associated infection and is not always associated with recent antibiotic use or hospital exposure.
  - Bloody diarrhea in afebrile patients should increase suspicion of E. coli 0157:H7. **No antibiotic therapy recommended since it may enhance toxin release and increase risk of hemolytic uremic syndrome (HUS).**
- Consider Campylobacter spp. in persons with travel history.

<table>
<thead>
<tr>
<th>CULTURE PENDING – NO clinical suspicion of HUS, C. difficile, or Sepsis (Treat for 5 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin 500 mg PO bid</td>
</tr>
<tr>
<td>Alternative</td>
</tr>
<tr>
<td>TMP/SMX 1 DS tab PO bid</td>
</tr>
</tbody>
</table>

*If travel history and suspicion of Campylobacter spp:*

- Clarithromycin 500 mg PO BID, OR Erythromycin 500 mg PO QID
- Alternative
- Ciprofloxacin 500 mg PO bid
Clostridium Difficile Infection (CDI)

The VIHA Antimicrobial Review Subcommittee has developed a bulletin that provides greater detail CDI on the treatment algorithm for adult and pediatric patients which can be accessed on the VIHA intranet at:

It can also be accessed from the VIHA Intranet Home Page by:
1. Selecting Clinical Resources from the banner.
2. Selecting Infectious Disease in the Quick Links section.

RISK FACTORS

Risk factors for CDI are generally divided into three main groups:

1. Host factors: age greater than 65 years; female sex; multiple comorbidities; immune compromised.
2. Disruption of normal intestinal microflora: antibiotic exposure within 3 months; medications affecting intestinal tract; loss of intestinal function (ileus, obstruction); chemotherapy; antacids/proton pump inhibitors; procedures (surgery, nasogastric tube, enemas).
3. Increased exposure to C. difficile: admission to hospital; admission to Long Term Care (LTC) facility; poor hand hygiene; infected hospital roommate; prior CDI episodes.

LAB DIAGNOSIS

- Patients with suspected CDI should have a stool sample submitted. Formed stool is not appropriate.
- In VIHA, the sample is first screened for C. difficile antigen. If the test is negative, no further testing is necessary. If the antigen test is positive then a second test is performed which is an enzyme immunoassay (EIA) test for C. difficile A and B toxins. The turnaround time (TAT) for this test is less than 24 hours and STAT tests can be arranged following consultation with the medical microbiologist on call.
- All positive tests are communicated to the ward for inpatients and to the physician’s office for outpatients.
- If the antigen test is positive but the toxin EIA assay is negative this generally indicates that the patient is colonized with a non-toxin-producing strain of C. difficile.
TREATMENT

Initial episode
- Mild-to-moderate infection:
  Metronidazole 500 mg orally 3 times daily (or 250 mg orally 4 times daily) for 10 to 14 days.
- Severe infection or unresponsiveness to or intolerance of metronidazole:
  Vancomycin 125 mg orally 4 times daily for 10 to 14 days.

First recurrence†
- Mild-to-moderate infection:
  Metronidazole 500 mg orally 3 times daily for 10 to 14 days.
- Severe infection or unresponsiveness to or intolerance of metronidazole:
  Vancomycin 125 mg orally 4 times daily for 10 to 14 days.

Second recurrence†
- Vancomycin 125 mg orally 4 times daily for 14 days.
- If patient has previously received vancomycin proceed to tapering therapy described below.

Third / subsequent recurrence(s)†
- Vancomycin in tapered and pulsed doses:
  - 125 mg orally 4 times daily for 14 days
  - 125 mg orally 2 times daily for 7 days
  - 125 mg orally once daily for 7 days
  - 125 mg orally once every 2 days for 14 days

PROBIOTICS †
- A probiotic agent such as *Saccharomyces boulardii* may be added, administered as 500 mg (2 x 250 mg capsules) orally 2 times daily for at least 4 weeks.
- Probiotic therapy may commence with the initiation of antimicrobial therapy. However, the efficacy of probiotics in preventing recurrent *C. difficile* infection is unclear because of inconsistent study results.
- Bacteremia or fungemia may rarely complicate the use of probiotics in immunocompromised or critically ill patients.
ADDED NOTES

- A paramount treatment principle is discontinuation of the inciting antibiotic as soon as possible.
- A positive toxin assay in a patient with minimal or no symptoms should NOT prompt treatment.
- Metronidazole and vancomycin show similar efficacy in patients with mild infection. Due to the risk of emergence of VRE as well as additional cost associated with vancomycin usage, **metronidazole remains the preferred agent in patients with mild-to-moderate infection.** Vancomycin may be considered as first-line therapy in patients who are greater than 75 years old, have comorbidities and/or who are immunosuppressed.
- Vancomycin is recommended as first-line therapy in patients with severe infection because of more prompt symptom resolution and lower risk of treatment failure. Determination of disease severity is left to clinician judgement and may include any or all of: a marked peripheral leukocytosis; renal dysfunction; severe abdominal pain; fever; hypotension; ileus; or toxic megacolon.
- Severely ill patients with ileus may have markedly delayed passage of oral antibiotics from the stomach to the colon. These individuals may benefit from the addition of intravenous metronidazole at a dose of 500 mg every eight hours.
- Surgery should be considered if the patient’s clinical status fails to improve. Toxic megacolon should be suspected if the patient develops abdominal distention with diminution of diarrhea; this may reflect paralytic ileus resulting from loss of colonic muscular tone.
- Not all patients with recurrent diarrhea following cessation of metronidazole or vancomycin therapy have recurrent CDI. Other conditions, such as post infectious irritable bowel syndrome, microscopic colitis or inflammatory bowel disease may be responsible.
- A 14-day course of metronidazole 500 mg PO TID costs approximately $4.00 versus a 14-day course of vancomycin 125 mg PO QID which costs approximately $400.

PREVENTION

Given the significant morbidity and mortality associated with CDI it is critical that appropriate measures be undertaken to prevent infection and transmission. A multifaceted approach of prudent antimicrobial use along with stringent infection control including hand washing with soap and water, early institution of contact precautions and disinfection of rooms with a bleach solution to kill spores are all essential in preventing CDI and controlling its spread.
Cholecystitis / Cholangitis

MILD SEVERITY
- Symptoms mirror minor biliary colic
  - DOES NOT require antimicrobial therapy

MODERATE SEVERITY or RISK
Severity criteria (one or more):
- Steady and severe pain (RUQ or epigastrum)
- Fever
- Leukocytosis

Additional Points:
- PRIOR ANTIBIOTIC USE in the last 3 months is a significant consideration in empiric therapy selection. A class effect needs to be considered.
- Anaerobic coverage (with metronidazole) is acknowledged to be controversial for moderate severity cholecystitis /cholangitis.
- Shorter durations of therapy should be encouraged when patients exhibit significant clinical improvement.
- Blood cultures recommended (particularly for cholangitis).

<table>
<thead>
<tr>
<th>USUAL PATHOGENS</th>
<th>Recommended Empiric Therapy (4 - 7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae Anaerobes</td>
<td>[Cefazolin 1 g IV q8h + Metronidazole 500 mg IV/PO q8h]</td>
</tr>
<tr>
<td>Enterococcus spp (not routinely covered for moderately severe infections)</td>
<td>Severe pen-allergy or cephalosporin allergy (e.g. anaphylaxis, angioedemia): [Ciprofloxacin 400 mg IV / 500 mg PO q12h + Metronidazole 500 mg IV/PO q8h]</td>
</tr>
</tbody>
</table>

SEVERE or HIGH RISK
Severity criteria:
- Septic presentation (includes the following):
  - Systemic inflammatory response syndrome (SIRS): hypothermia or fever; tachycardia; tachypnea or hypocapnia (arterial CO2 less than 32 mm Hg); and leukopenia or leukocytosis.
  - Evidence of organ dysfunction, hypotension (low blood pressure), or hypoperfusion to 1 or more organs.
Arterial hypotension or hypoperfusion is responsive to adequate fluid resuscitation. If unresponsive see empiric therapy for SEPTIC SHOCK below.

High Risk criteria (one or more):
- Healthcare-associated infection.
- Recent ERCP or stent in place.
- Patient has bili-enteric anastomosis, e.g. post pancreaticoduodenectomy (Whipple’s procedure).
- Liver transplant.
- Those requiring enterococcal coverage such as:
  - Antimicrobial exposure in the last 90 days to cephalosporins and other broad-spectrum regimens selecting for enterococci.
  - With valvular heart disease or intravascular prosthetic devices.
  - Severe immunosuppression (e.g. solid organ transplant, or high-dose steroids).

Additional Points
- PRIOR ANTIBIOTIC USE in the last 3 months is a significant consideration in empiric therapy selection. A class effect needs to be considered.
- Blood cultures recommended (high risk of bacteremia).
- Drainage of obstructed biliary tree is essential for therapy of cholangitis.
- The severely ill patient with cholangitis may take slightly longer to resolve compared to the surgically treated cholecystitis patient.

<table>
<thead>
<tr>
<th>USUAL PATHOGENS</th>
<th>Recommended Empiric Therapy (7 – 10 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td>Duration should be guided by intraoperative findings and clinical response and should be no more than 7 days in most cases.</td>
</tr>
<tr>
<td>Enterococcus spp</td>
<td>Piperacillin-tazobactam 3.375 g IV q6h</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>Penicillin allergic (clear history):</td>
</tr>
<tr>
<td></td>
<td>[Ciprofloxacin 400 mg IV q12h + Metronidazole 500 mg IV q8h + Vancomycin 15 mg/kg (round to nearest 250 mg) IV q12h]. Adjust vancomycin interval based on GFR.</td>
</tr>
</tbody>
</table>
SEPTIC SHOCK
Criteria (includes all of the following):
• Systemic inflammatory response syndrome (SIRS) which includes hypothermia or fever; tachycardia; tachypnea or hypocapnia (arterial CO2 less than 32 mm Hg); and leukopenia or leukocytosis.
• Evidence of organ dysfunction, hypotension (low blood pressure), or hypoperfusion to 1 or more organs.
• Arterial hypotension or hypoperfusion (despite adequate fluid resuscitation) resulting in the need for vasopressors.

Additional Points:
• Implement antibiotics immediately. Broad-spectrum agents should be infused first.
• Consult intensive care.

<table>
<thead>
<tr>
<th>Recommended Empiric Therapy (7 – 10 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration should be guided by intra-operative findings and clinical response and should be no more than 7 days in most cases.</td>
</tr>
<tr>
<td>Imipenem 500 mg IV q6h + Vancomycin 20 mg/kg (round to nearest 250 mg) x 1 dose, then 15 mg/kg (round to nearest 250 mg) IV q12h. Adjust vancomycin interval based on GFR.</td>
</tr>
<tr>
<td>Severe pen-allergy or cephalosporin allergy (e.g. anaphylaxis, angioedemia): Ciprofloxacin 400 mg IV q12h + Gentamicin 2 mg/kg IV x STAT (further dosing to be reassessed by the attending intensivist) + Metronidazole 500 mg IV q8h + Vancomycin 20 mg/kg (round to nearest 250 mg) x 1 dose, then 15 mg/kg (round to nearest 250 mg) IV q12h. Adjust interval based on GFR.]</td>
</tr>
</tbody>
</table>
Pancreatitis

Several classifications exist for prediction of acute pancreatitis severity. A commonly used classification system (the Atlanta classification) divides acute pancreatitis into two broad categories:

1. Mild (edematous and interstitial acute) pancreatitis.
2. Severe (usually synonymous with acute necrotizing) pancreatitis.

For detailed guidance on staging please refer to VIHA online resources such as Up-To-Date.

**MILD – MODERATE**

- No prophylactic or empiric antibiotic therapy is required unless there is a documented infection.

**SEVERE**

- The administration of prophylactic antibiotics to patients with severe necrotizing pancreatitis prior to the diagnosis of infection is NOT recommended.
- Initiate antimicrobial therapy in proven secondary infection or when the patient is hemodynamically unstable and requiring vasopressors.
- It is not possible to differentiate necrotizing pancreatitis from infected necrotizing pancreatitis on the basis of a CT scan alone. Fine needle aspirate is required.
- Surgical debridement and drainage with culture is essential for established infections.
- Blood cultures recommended (high risk of bacteremia).

<table>
<thead>
<tr>
<th>USUAL PATHOGENS</th>
<th>Recommended Empiric Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Duration based on clinical improvement)</td>
</tr>
<tr>
<td>Enterobacteriaceae Enterobacter spp S. aureus Coagulase negative Staph Anaerobes</td>
<td>Piperacillin-tazobactam 3.375 g IV q6h OR Imipenem 500 mg IV q6h Penicillin allergic (clear history) [Ciprofloxacin 400 mg IV q12h Metronidazole 500 mg IV q8h + Vancomycin 15 mg/kg (round to nearest 250 mg) IV q12h]. Adjust vancomycin interval based on GFR.</td>
</tr>
</tbody>
</table>
Diverticulitis

MILD-MODERATE

- Generally considered to be uncomplicated acute diverticulitis. See definition of complicated acute diverticulitis below under SEVERE.
- Typically managed on an ambulatory basis with oral therapy.
- The decision to manage on an outpatient basis depends on several factors including the severity of presentation, the ability to tolerate oral intake, and the presence of comorbid diseases.
- Duration directed by clinical response.

<table>
<thead>
<tr>
<th>USUAL PATHOGENS</th>
<th>Recommended Empiric Therapy (4 – 7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POLYMICROBIAL:</td>
<td></td>
</tr>
<tr>
<td>- Enterobacteriaceae</td>
<td></td>
</tr>
<tr>
<td>- Anaerobes</td>
<td></td>
</tr>
<tr>
<td>- Enterococcus spp*</td>
<td></td>
</tr>
<tr>
<td>Oral Preferred</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin-clavulanate 500 mg PO TID</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>[TMP/SMX 1 DS tab PO BID + Metronidazole 500 mg PO TID] OR</td>
<td></td>
</tr>
<tr>
<td>[Ciprofloxacin 500 mg PO BID + Metronidazole 500 mg PO TID]</td>
<td></td>
</tr>
<tr>
<td>IV Regimen (if initially unable to take orally)</td>
<td></td>
</tr>
<tr>
<td>[Ceftriaxone 1 g IV q24h plus/minus Metronidazole 500 mg IV q8h] Switch to one of the above oral regimens when able to tolerate.</td>
<td></td>
</tr>
</tbody>
</table>

* Coverage of Enterococcus is controversial. Only amoxicillin-clavulanate covers Enterococcus.
SEVERE
- Requires hospitalization.
- Includes:
  - Complicated diverticulitis (i.e. patients with perforation, obstruction, an abscess, or fistula).
  - Uncomplicated diverticulitis in the frail elderly, immunosuppressed, those with significant comorbidities, and those with high fever or significant leukocytosis.
- Duration directed by clinical response.

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Recommended Empiric Therapy (7 – 10 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POLYMICROBIAL:</td>
<td></td>
</tr>
<tr>
<td>- Enterobacteriaceae</td>
<td></td>
</tr>
<tr>
<td>- Anaerobes</td>
<td></td>
</tr>
<tr>
<td>- Enterococcus spp*</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Piperacillin-tazobactam</strong> 3.375 g IV q6h</td>
</tr>
<tr>
<td></td>
<td><strong>Penicillin allergic</strong> (clear history)</td>
</tr>
<tr>
<td></td>
<td>[<strong>Ciprofloxacin</strong> 400 mg IV q12h]</td>
</tr>
<tr>
<td></td>
<td><strong>Metronidazole</strong> 500 mg IV q8h +</td>
</tr>
<tr>
<td></td>
<td><strong>Vancomycin</strong> 15 mg/kg (round to nearest 250 mg) IV q12h]. Adjust vancomycin interval based on GFR.</td>
</tr>
</tbody>
</table>

Cirrhotic Patients with Active Upper GI Bleed

Patients with cirrhosis who present with upper GI bleeding (from varices or other causes) should be given prophylactic antibiotics, preferably before endoscopy (although effectiveness has also been demonstrated when given after endoscopy).

<table>
<thead>
<tr>
<th>Recommended Prophylactic Regimen (Continue for 7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ceftriaxone</strong> 1g IV q24h</td>
</tr>
</tbody>
</table>

*If severe pen-allergy or cephalosporin allergy (e.g. *anaphylaxis*, *angioedemia*): Consult Medical Microbiologist or Infectious Disease physician.*
Peritonitis – Spontaneous Bacterial (Primary)

Is typically defined as a group of diseases with different causes, having in common only an infection in the peritoneal cavity without an obvious source of peritoneal contamination, such as in patients with chronic liver disease and ascites.

- Take blood and peritoneal fluid cultures.
- Spontaneous bacterial peritonitis (SBP) is typically monomicrobial. Polymicrobial infections suggest bowel perforation – see secondary peritonitis.

<table>
<thead>
<tr>
<th>USUAL PATHOGENS</th>
<th>Recommended Empiric Therapy (5-7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td>Ceftriaxone 1 g IV q24h</td>
</tr>
<tr>
<td>Occassionally:</td>
<td></td>
</tr>
<tr>
<td>- S. pneumoniae</td>
<td>Oral (sequential therapy) regimens</td>
</tr>
<tr>
<td>- Streptococcus spp.</td>
<td>Amoxicillin-clavulanate 500 mg PO TID</td>
</tr>
<tr>
<td></td>
<td>Penicillin allergic (clear history):</td>
</tr>
<tr>
<td></td>
<td>TMP/SMX 1 DS tab PO BID</td>
</tr>
</tbody>
</table>
**Peritonitis – Secondary**

Refers to infections that arise from microbes in the alimentary tract – due to perforation of a hollow viscus causing contamination of the otherwise sterile peritoneal cavity.

**USUAL PATHOGENS – POLYMICROBIAL**
- Enterobacteriaceae
- Anaerobes
- Enterococcus spp (routine coverage typically not required)

**MILD to MODERATE**

*Severity criteria (one or more):*
- Steady and severe pain (RUQ or epigastrum)
- Fever
- Leukocytosis

**Additional Points:**
- PRIOR ANTIBIOTIC USE in the last 3 months is a significant consideration in empiric therapy selection. A class effect needs to be considered.
- **Shorter durations of therapy** should be encouraged when patients exhibit significant clinical improvement.
- Obtain blood cultures.

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<tr>
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</tr>
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<tbody>
<tr>
<td>Enterobacteriaceae Anaerobes</td>
<td>Cefazolin 1 g IV q8h + Metronidazole 500 mg IV/PO q8h</td>
</tr>
<tr>
<td>Enterococcus spp (not routinely covered for moderately severe infections)</td>
<td>Severe pen-allergy or cephalosporin allergy (e.g. anaphylaxis, angioedemia): Ciprofloxacin 400 mg IV / 500 mg PO q12h + Metronidazole 500 mg IV/PO q8h</td>
</tr>
</tbody>
</table>
SEVERE
Severity criteria:
- Septic presentation (includes the following):
  - Systemic inflammatory response syndrome (SIRS): hypothermia or fever; tachycardia; tachypnea or hypocapnia (arterial CO2 less than 32 mm Hg); and leukopenia or leukocytosis.
  - Evidence of organ dysfunction, hypotension (low blood pressure), or hypoperfusion to 1 or more organs.
  - Arterial hypotension or hypoperfusion is responsive to adequate fluid resuscitation. If unresponsive – see empiric therapy for SEPTIC SHOCK below.

High Risk criteria (one or more):
- Healthcare-associated infection.
- Those requiring enterococcal coverage such as:
  - Antimicrobial exposure in the last 90 days to cephalosporins and other broad-spectrum regimens selecting for enterococci.
  - With valvular heart disease or intravascular prosthetic devices.
  - Severe immunosuppression (e.g. solid organ transplant, or high-dose steroids).

Additional Points
- PRIOR ANTIBIOTIC USE in the last 3 months is a significant consideration in empiric therapy selection. A class effect needs to be considered.
- Blood cultures recommended (high risk of bacteremia).

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</tr>
<tr>
<td>Anaerobes</td>
<td></td>
</tr>
</tbody>
</table>
SEPTIC SHOCK

Criteria (includes all of the following):

- Systemic inflammatory response syndrome (SIRS) which includes hypothermia or fever; tachycardia; tachypnea or hypocapnia (arterial CO2 less than 32 mm Hg); and leukopenia or leukocytosis.
- Evidence of organ dysfunction, hypotension (low blood pressure), or hypoperfusion to 1 or more organs.
- Arterial hypotension or hypoperfusion (despite adequate fluid resuscitation) resulting in the need for vasopressors.

Additional Points:

- Implement antibiotics immediately. Broad-spectrum agents should be infused first.
- Consult intensive care.

---

**Recommended Empiric Therapy (7 – 10 days)**

Duration should be guided by intra-operative findings and clinical response and should be no more than 7 days in most cases.

<table>
<thead>
<tr>
<th>Imipenem</th>
<th>Vancomycin 20 mg/kg (round to nearest 250 mg) x 1 dose, then 15 mg/kg (round to nearest 250 mg) IV q12h. Adjust interval based on GFR.</th>
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<td>Ciprofloxacin 400 mg IV q12h + Gentamicin 2 mg/kg IV x STAT (further dosing to be reassessed by the attending intensivist) + Metronidazole 500 mg IV q8h + Vancomycin 20 mg/kg (round to nearest 250 mg) x 1 dose, then 15 mg/kg (round to nearest 250 mg) IV q12h. Adjust interval based on GFR.</td>
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