Comité de gérance des antimicrobiens
Anti-Infective Stewardship Committee

Optimal antimicrobial care for our patients and our future

Thérapie antimicrobienne optimale pour nos patients et notre avenir

Antimicrobial Treatment Guidelines for Common Infections

June 2016

Published by:
The NB Provincial Health Authorities Anti-infective Stewardship Committee under the direction of the Drugs and Therapeutics Committee

Introduction:

These clinical guidelines have been developed or endorsed by the NB Provincial Health Authorities Anti-infective Stewardship Committee and its Working Group, a sub-committee of the New Brunswick Drugs and Therapeutics Committee. Local antibiotic resistance patterns and input from local infectious disease specialists, medical microbiologists, pharmacists and other physician specialists were considered in their development.

These guidelines provide general recommendations for appropriate antibiotic use in specific infectious diseases and are not a substitute for clinical judgment.

Website Links

For Horizon Physicians and Staff:
http://skyline/patientcare/antimicrobial

For Vitalité Physicians and Staff:

http://boulevard/FR/patientcare/antimicrobial

To contact us: antimicrobial.stewardship@rha-rrs.ca

When prescribing antimicrobials:

- Carefully consider if an antimicrobial is truly warranted in the given clinical situation
- Consult local antibiograms when selecting empiric therapy
- Include a documented indication, appropriate dose, route and the planned duration of therapy in all antimicrobial drug orders
- Obtain microbiological cultures before the administration of antibiotics (when possible)
- Reassess therapy after 24-72 hours to determine if antibiotic therapy is still warranted or effective for the given organism or clinical situation. Reassess based on relevant clinical data, microbiologic and/or radiographic information
- Assess for de-escalation as appropriate based on available microbiology culture and susceptibility results

Antimicrobial Treatment Guidelines For Common Infections

(Click arrow buttons ➲ to navigate)

EMPIRIC ANTIMICROBIAL THERAPY FOR DIABETIC FOOT INFECTION

(Endorsed by NB Health Authorities Anti-Infective Stewardship Committee February 2016)

Infection Severity	Preferred Empiric Regimens[1]	Alternative Regimens[1]	Comments
Mild • Cellulitis **less than 2 cm** and without involvement of deeper tissues • Non-limb threatening • No signs of systemic toxicity	Wound **less than 4 weeks** duration • cephalexin 500 mg PO four times daily* Wound **greater than 4 weeks** duration • sulfamethoxazole/trimethoprim 800/160 mg PO twice daily* + metroNIDAZOLE 500 mg PO twice daily	Wound **less than 4 weeks** duration • clindamycin 300 – 450 mg PO four times daily (only if severe β-lactam allergy) Wound **greater than 4 weeks** duration • amoxicillin/clavulanate 875/125mg PO twice daily* **OR** • doxycycline 100 mg PO twice daily + metroNIDAZOLE 500 mg PO twice daily	• Outpatient management recommended • Tailor regimen based on C&S results & patient response
Moderate • Cellulitis **greater than 2 cm** or involvement of deeper tissues • Non-limb threatening • No signs of systemic toxicity	Wound **less than 4 weeks** duration • ceFAZolin 2 g IV q8h* **OR** • cefTRIAXone 2 g IV once daily (to facilitate outpatient management when ambulatory administration of ceFAZolin not possible) Wound **greater than 4 weeks** duration • ceFAZolin 2 g IV q8h* + metroNIDAZOLE 500 mg PO twice daily **OR** • cefTRIAXone 2 g IV once daily + metroNIDAZOLE 500 mg PO twice daily (to facilitate outpatient management when ambulatory administration of ceFAZolin not possible)	Wound **less than 4 weeks** duration • levofloxacin 750mg IV/PO once daily* (only if severe β-lactam allergy) Wound **greater than 4 weeks** duration • levofloxacin 750mg IV/PO once daily* + metroNIDAZOLE 500 mg PO twice daily (only if severe β-lactam allergy)	• Initial management with outpatient parenteral therapy with rapid step-down to oral therapy after 48 to 72 hours based on patient response recommended • Tailor regimen based on C&S results & patient response
Severe • Systemic signs of sepsis • Limb or foot threatening • Extensive soft tissue involvement • Pulseless foot	• piperacillin-tazobactam 3.375 g IV q6h*	• imipenem/cilastatin 500 mg IV q6h* **OR** • levofloxacin 750 mg IV once daily* + metroNIDAZOLE 500 mg PO/IV twice daily (only if severe β-lactam allergy)	• Inpatient management recommended • Urgent vascular assessment if pulseless foot • Tailor regimen based on C&S results & patient response

Clinical Pearls:

[1] If high risk for MRSA, should include sulfamethoxazole/trimethoprim 800/160 mg PO twice daily * or doxycycline 100 mg PO twice daily for mild infections and vancomycin weight-based dosing to a target trough of 15 – 20 mg/L for moderate-severe infections

- Debridement, good glycemic control and proper wound care are important for the management of diabetic foot infections
- Cultures: prefer tissue specimens post-debridement and cleansing of wound; surface or wound drainage swabs not recommended
- In a clinically infected wound a positive probe-to-bone (PTB) test is highly suggestive of osteomyelitis
- Imaging: recommend plain radiography (radionuclide imaging unnecessary)

Duration of Therapy

- Soft tissue only – 2 weeks
- Bone involvement with complete surgical resection of all infected bone – 2 weeks
- Bone involvement with incomplete surgical debridement of infected bone – 4-6 weeks IV
- Bone involvement with no surgical debridement or residual dead bone postoperatively – 6 weeks IV, followed by 6 weeks PO

References:

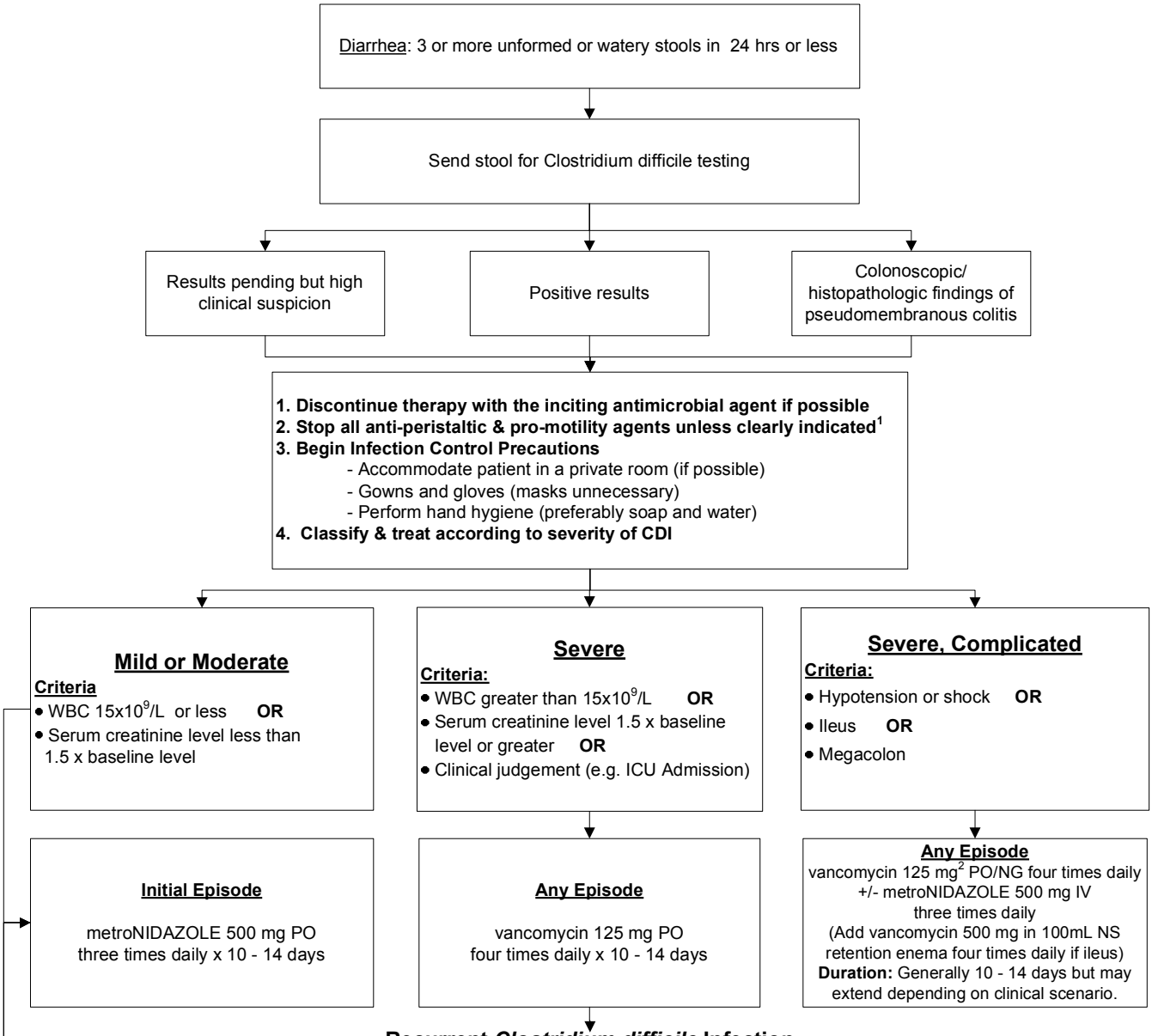
1. Bowering K, Embil JM. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Foot Care. Can J Diabetes 37(2013) S145-S149
2. Lipsky BA, Berendt AR, Cornia PB *et al.* 2012 Infectious Disease Society of America Clinical Practice Guidelines for the Diagnosis and Treatment of Diabetic Foot Infections. CID 2012:54(12):132-173
3. Lipsky BA, Armstrong DG, Citron DM *et al.* Ertapenem versus piperacillin/tazobactam for diabetic foot infections (SIDESTEP): prospective, randomized, controlled, double-blinded, multicentre trial. Lancet 2005; 366:1695 – 1703
4. Blond-Hill E, Fryters S. Bugs & Drugs An Antimicrobial/Infectious Diseases Reference. 2012. Alberta Health Services

* Dose adjustment required in renal impairment

9782-10650-04-2016

Antimicrobial Management of *Clostridium difficile* Infection (CDI)

(NB Provincial Health Authorities Anti-Infective Stewardship Committee, May 2014)



Recurrent *Clostridium difficile* Infection

First Recurrence:
Treat same as for initial episode and according to CDI severity

Second Recurrence:
Vancomycin taper regimen: 125 mg PO four times daily x 14 days, then 125 mg PO twice daily x 7 days, then 125 mg PO once daily x 7 days, then 125 mg PO every 2 days x 2 weeks then discontinue

Third Recurrence:
Consider ID consult

Clinical Pearls

- Pregnancy/breast feeding: use vancomycin PO (avoid metroNIDAZOLE)
- Symptoms of CDI usually begin 2 - 3 days after colonization
- Test for cure is not recommended
- Vancomycin administered intravenously is ineffective for CDI
- Fidaxomicin is a non-formulary item that should only be considered under extenuating clinical circumstances, ID consultation required

[1]Examples: loperamide, diphenoxylate, opioids, metoclopramide, domperidone, etc

[2]For complicated severe episodes some authorities recommend vancomycin doses up to 500 mg; appropriate dose has not been established in clinical trials

Adapted from: Vancouver Coastal Health Antimicrobial Stewardship Treatment Guidelines for Common Infections March 2011 1st Edition

Antimicrobial Therapy for Intra-Abdominal Infections

(NB Provincial Health Authorities Anti-Infective Stewardship Committee, November 2015)

Origin/Severity of Intra-Abdominal Infection	Probable Pathogens	Preferred Empiric Regimens	Alternative Empiric Regimens	Comments
Community Acquired Infection, Mild to Moderate severity: • i.e. gastroduodenal perforation, cholangitis[a], cholecystitis[a], appendicitis, diverticulitis[b], primary (spontaneous) bacterial peritonitis • With no evidence of systemic toxicity (APACHE II score less than 15)	**Core:** Enterobacteriaceae (i.e. *E.coli, Klebsiella spp, Proteus spp, Enterobacter spp.*) Anaerobes (i.e. *B. fragilis*, *Clostridium spp.* etc…), *Streptococcus spp,* ± *Enterococcus* spp (see below if isolated)	ceFAZolin 2 g IV q8h[g,*] + metroNIDAZOLE 500 mg IV/PO q12h[a,b] **Intravenous-to-Oral Conversion[c]:** amoxicillin/clavulanate 875/125 mg po q12h[h,*]	CefOXitin 2 g IV q6h[h,*] **OR** gentamicin 5 – 7 mg/kg IV q24h* + metroNIDAZOLE 500 mg IV/PO q12h **OR** ciprofloxacin 400 mg IV OR 500 mg PO q12h* + metroNIDAZOLE 500 mg IV/PO q12h	**Duration of Therapy, dependent on clinical picture:** o 5 – 7 days usually sufficient if optimal source control obtained o If intra-abdominal abscess: antimicrobial therapy may be prolonged, with duration dependant on resolution (up to 4 to 6 weeks) o Day of intervention (drainage, surgery, etc.) considered as day 1 of therapy **Stop antimicrobial within 24 hours if**: o acute stomach, duodenum &/or proximal jejunum perforation if no acid-reducing therapy or malignancy and source control achieved **OR** o penetrating bowel trauma repaired within 12 hours **OR** o intraoperative contamination of a surgical field from enteric contents **OR** o acute appendicitis without perforation, abscess or local peritonitis **OR** o patients undergoing cholecystectomy for acute cholecystitis unless evidence of infection outside wall of the gallbladder (ex. perforation)
Community Acquired Infection, Severe: • As above with APACHE II score greater than or equal to 15, signs of systemic toxicity, greater than 70 years old, immunocompromised, secondary peritonitis, cancer, poor nutritional status or incomplete or delayed source control	**Core**	cefTRIAXone 2 g IV q24h[g] + metroNIDAZOLE 500 mg IV/PO q12h **Intravenous-to-Oral Conversion[c]:** As for mild to moderate above	piperacillin/tazobactam 3.375 g IV q6h[d,e,h,*] **OR** ampicillin 2 g IV q6h[h,*] + gentamicin 5 – 7 mg/kg IV q24h* + metroNIDAZOLE 500 mg IV q12h **OR** ciprofloxacin 400 mg IV q12h* + metroNIDAZOLE 500 mg IV q12h	
Healthcare Associated • Hospitalized greater than 48 hours at time of onset, recent prolonged hospitalization, post-operative infection, long term care, rehab, dialysis, nursing home, **recent antibiotics**	**Core Plus:** Pseudomonas, Multidrug Resistant (MDR) Gram-negative bacteria, MRSA (see below if isolated)	piperacillin/tazobactam 3.375 g IV q6h[d,e,h,*]	imipenem-cilastin 500 mg IV q6h[e,g,*] (preferred if suspected MDR Gram-negative) **OR** ciprofloxacin 400 mg IV q12h* + metroNIDAZOLE 500 mg IV q12h + vancomycin 15 mg /kg IV q12h[f,*]	

(continued on next page)

Origin/Severity of Intra-Abdominal Infection	Probable Pathogens	Preferred Directed Regimens	Alternative Directed Regimens	Comments
If MRSA Suspected (colonized or history of MRSA infection)		Add vancomycin 15 mg/kg IV q12h* (for target trough of 15 – 20 mg/L)		
If Candida isolated		Add fluconazole 800 mg IV/PO then 400 mg IV/PO q24h*	micafungin 100 mg IV q24h	• micafungin preferred if *Candida krusei* or *Candida glabrata* isolated
If Enterococci isolated		Add ampicillin 2 g IV q6h[h,*] (not required if on piperacillin/tazobactam or imipenem-cilastin)	**Immediate (IgE-mediated) penicillin allergy or penicillin resistant:** vancomycin 15 mg/kg IV q12h[f,*]	• Enterococcal coverage only necessary if: ➢ isolated as predominant organism in culture **OR** ➢ healthcare associated infection **OR** ➢ patient is immunocompromised **OR** ➢ Blood culture positive • If *Enterococcus faecium* isolated and criteria for treatment met, use vancomycin as empiric therapy and reassess based on susceptibility results

Clinical Pearls:

- Antimicrobial therapy does not preclude source control (ex. percutaneous drainage or surgery)
- Patients with recent prolonged hospitalization (5 or more days) or recent antimicrobials (2 or more days) within the previous 3 months pose risk for resistance and treatment failure, treat as healthcare associated
- Empiric Enterococci coverage is not recommended for mild-moderate severity community-acquired intra-abdominal infections. It should be reserved for patients in whom this pathogen is more frequently found (healthcare-associated infections, particularly those with postoperative infection, presence of severe immunosuppression, recurrent infection, patients who receive long-term cephalosporin treatment, and those with valvular heart disease or prosthetic intravascular materials)
- CAUTION: Significant *E.coli* resistance (greater than 20%) to fluoroquinolones and amoxicillin exist in some areas of the province; check local antibiogram and confirm C&S results when available
- Pathogen directed therapy should be used when culture and susceptibility results are available

Workup:

- Recommend blood, intraoperative and/or abscess fluid cultures in patients with post-operative or healthcare-associated infections; those with treatment failure and/or requiring re-operation; or recently on antimicrobial therapy
- Blood cultures recommended if patient has sepsis syndrome
- Reassess initial empiric therapy based on clinical state & results of microbiological analysis

[a] Anaerobic coverage not indicated for cholecystitis & cholangitis unless biliary-enteric anastomosis is present or aggravating factors (advanced age, immunosuppression or metabolic instability)

[b] Most cases of diverticulitis can be managed with oral antibiotic therapy

[c] Intravenous-to-Oral conversion: consider if infection well controlled, afebrile x 24 hrs., hemodynamically stable, tolerating oral intake and no clinical, radiographic or surgical sign of intra-abdominal collection from non-optimal drainage

[d] For *Pseudomonas aeruginosa* infection, piperacillin/tazobactam dosage may be increased to 4.5 gm IV q6h

[e] Anaerobic coverage adequate, addition of metroNIDAZOLE or clindamycin to piperacillin/tazobactam or imipenem-cilastin not necessary

[f] Adjust vancomycin dose to target a trough level of 10 to 20 mg/L

[g] Appropriate therapy option for patients with an immediate Type-1 (IgE-mediated) hypersensitivity reaction to penicillin (i.e. anaphylaxis, angioedema, laryngeal edema, urticaria)

[h] Avoid in patients with immediate Type-1 (IgE-mediated) hypsensitivity reaction to penicillin, significant risk of cross-reactivity exists.

*Dose adjustment required in renal impairment

Antimicrobial Therapy for Acute Bacterial Rhinosinusitis (ABRS)

(NB Provincial Health Authorities Anti-Infective Stewardship Committee, November 2015)

Treatment Criteria

- **Clinical diagnosis and differentiation of acute bacterial from viral rhinosinusitis is based on the characteristic patterns of clinical presentations taking into account duration of symptoms, severity of illness, temporal progression and "double-sickening" in the clinical course**
- **The following clinical presentations (any of the 3) are recommended for identifying patients with acute bacterial vs. viral rhinosinusitis:**
  1. Onset with persistent symptoms or signs compatible with acute rhinosinusitis, lasting for greater than or equal to 10 days without any evidence of clinical improvement
  2. Onset with severe symptoms or signs of high fever (greater than or equal to 39 °C) and purulent nasal discharge or facial pain lasting for at least 3 to 4 consecutive days at the beginning of illness
  3. Onset with worsening symptoms or signs characterized by the new onset of fever, headache or increased in nasal discharge following a typical viral upper respiratory infection that lasted 5 – 6 days and were initially improving ("double sickening")
- **Initiation of empiric antimicrobial therapy is recommended as soon as the clinical diagnosis of ABRS is established based on the above criteria; if diagnosis is uncertain due to mild symptoms then consider observing without antibiotic therapy for 3 days**

Presentation	Preferred Empiric Regimen	Alternative Empiric Regimen	Duration	Comments
Mild – Moderate Symptoms less than 10 days duration	Symptomatic therapy only Consider intranasal saline irrigation		5 – 7 days	+/- intranasal corticosteroids
Mild – Moderate Symptoms greater than 10 days OR worsening after 5 to 6 days OR Severe Symptoms for 3 to 4 consecutive days	doxycycline 100 mg po q12h	amoxicillin 1000 mg po q8h* **OR** amoxicillin/clavulanate 875/125 mg po q12h* **OR** sulfamethoxazole/trimethoprim 800/160 mg po q12h*		• Consider adjunctive intranasal saline irrigation • Consider adjunctive intranasal corticosteroids in patients with a history of allergic rhinitis • If a patient has been on antibiotic therapy in the past month the antimicrobial therapy chosen should be based on a different mechanism of action regardless of the clinical success
Failure of Initial Therapy (symptoms worsening after 48 – 72 hrs. or failure to improve after 3 – 5 days of initial empiric antimicrobial therapy)	amoxicillin/clavulanate 875/125 mg po q12h* + amoxicillin 1000 mg po q12h* (high-dose amoxicillin with clavulanate)	levofloxacin 500 mg po q24h* **OR** cefuroxime 500 mg po q12h*		• Consider adjunctive intranasal saline irrigation • Consider adjunctive intranasal corticosteroids in patients with a history of allergic rhinitis • Patients who fail to respond should be assessed for possible causes including infection with resistant organism, inadequate dosing and noninfectious cause • Select an agent with broader spectrum of activity and from a different antimicrobial class

Clinical Pearls

- **Compatible Signs and Symptoms:** purulent nasal discharge; nasal congestion or obstruction; facial swelling, congestion or fullness; facial pain or pressure; fever; hyposmia or anosmia; or dental pain
- Majority of cases of acute sinusitis are viral and resolve within 5 to 7 days without the need for antibiotics; only 0.5 – 2% of viral upper respiratory infections are complicated by bacterial infection
- Colour of nasal discharge or sputum is related to the presence of neutrophils, not bacteria, and should not be used to diagnose bacterial rhinosinusitis
- Macrolides are not recommended for empiric therapy due to growing resistance rates for *Streptococcus pneumoniae* and *Haemophilus influenzae* within the Province
- Respiratory fluoroquinolones (e.g. levofloxacin, moxifloxacin) should be reserved for failure of first-line options due to the potential for increasing resistance, risk of *Clostridium difficile* infection and their importance in the management of other infections
- Respiratory fluoroquinolones (e.g. levofloxacin, moxifloxacin) have not been found to be superior to β-lactams in the management of ABRS
- Antibiotics have not been shown to be beneficial in chronic rhinosinusitis without acute clinical deterioration
- Consider ID consultation for refractory nosocomial rhinosinusitis
- Decongestants (topical or oral) and/or antihistamines are not recommended as adjunctive therapy

*Dose adjustment required in renal impairment

Antimicrobial Therapy for Acute Exacerbation of Chronic Obstructive Pulmonary Disease

(NB Provincial Health Authorities Anti-Infective Stewardship Committee, November 2015)

Treatment Criteria

- The use of antibiotics in acute exacerbations of chronic obstructive pulmonary disease (AECOPD) is controversial
- Antimicrobial therapy is only recommended when AECOPD are accompanied by all 3 cardinal symptoms or at least 2 of the 3 cardinal symptoms, if increased sputum purulence is one of the 2 symptoms:
  1. Increased dyspnea
  2. Increased sputum volume
  3. Increased sputum purulence
- Patients receiving invasive or non-invasive ventilation for AECOPD should be initiated on intravenous antimicrobial therapy
- Antibiotic selection should be based on patient symptoms and risk factors
- If infiltrate on chest x-ray or pneumonia suspected then treat as per pneumonia treatment guidelines

Risk Stratification	Probable Organism	Preferred Empiric Regimen	Alternative Empiric Regimens	Duration	Comments
Acute Bronchitis • patients presenting with only 1 of the 3 cardinal symptoms	Viral in most cases	Antimicrobial therapy **not** recommended Symptomatic therapy only			
Simple (Low-Risk Patients) • Less than 4 exacerbations per year	*Streptococcus pneumoniae* *Haemophilus influenzae* *Moraxella catarrhalis*	doxycycline 100 mg po q12h	amoxicillin/clavulanate 875/125 mg po q12h* **OR** sulfamethoxazole/trimethoprim 800/160 mg po q12h* **OR** cefuroxime 500 mg po q12h* **OR** clarithromycin 500 mg po q12h	5 days	• If a patient has received an antibiotic in the last 3 months the therapy chosen should be a regimen based on a different mechanism of action regardless of the clinical success • Tailor antibiotic therapy for sputum culture results if available
Complicated (High Risk Patients) At least one of: • Forced expiratory volume in 1 second (FEV_1) less than 50% predicted • Greater than or equal to 4 exacerbations per year • Ischemic heart disease • Use of home oxygen • Chronic steroid use	As in simple plus: Klebsiella spp and other Gram-negatives, Increased probability of beta-lactam resistance	Oral Therapy: amoxicillin/clavulanate 875/125 mg po q12h* Intravenous Therapy: cefTRIAXone 1-2 g IV q24h	Oral Therapy: cefuroxime 500 mg po q12h* **OR** clarithromycin 500 mg po q12h* **OR** levofloxacin 750 mg po q24h* Intravenous Therapy: levofloxacin 750 mg IV q24h*	5 – 10 days 5 days (for levofloxacin)	• If a patient has received an antibiotic in the last 3 months the therapy chosen should be a regimen based on a different mechanism of action regardless of the clinical success • Tailor antibiotic therapy for sputum culture results if available
Bronchiectasis/ End-stage Lung Disease	As in simple and complicated plus: *Pseudomonas aeruginosa,* *Staphylococcus aureus,* MRSA Other non-fermenting Gram negative bacilli	Oral Therapy: amoxicillin/clavulanate 875/125 mg po q12h* **±** ciprofloxacin 500 -750 mg po q12h* (if *Pseudomonas aeruginosa* is suspected) Intravenous Therapy: cefTRIAXone 1-2 g IV q24h **OR** piperacillin/tazobactam 4.5 g IV q6h* (if *Pseudomonas aeruginosa* is suspected)	Oral Therapy: levofloxacin 750 mg po q24h* Intravenous Therapy: levofloxacin 750 mg IV q24h*	7 – 14 days	• **Tailor antibiotic therapy for sputum culture results (past or current)**

Clinical Pearls

- Macrolides are not recommended as first line empiric therapy due to growing resistance rates for *Streptococcus pneumoniae* and *Haemophilus influenzae*
- Fluoroquinolones should be reserved for only severe cases, failure of first line options or β-lactam allergy in complicated cases due to the potential for increasing resistance, risk of *Clostridium difficile* infection and their importance in the management of other infections
- Empiric therapy for atypical organisms (*Mycoplasma pneumoniae* & *Chlamydophilia pneumoniae*) not recommended
- Consider obtaining cultures if not improving after 72 hours of antimicrobial therapy
- Consider systemic corticosteroids for moderate to severe exacerbations of COPD (prednisone 40 mg po once daily for 5 days)
- Influenza vaccination and pneumococcal vaccination recommended

*Dose adjustment required in renal impairment

Antimicrobial Therapy for Adult Community Acquired Pneumonia¶

(NB Provinical Health Authorities Anti-Infective Stewardship Committee, November 2014)

Treatment Considerations:

• Having taken antibiotics within the past 3 months significantly increases the risk of resistant *S. pneumoniae*. Choose an antibiotic from a different class

¶Exclusion: patient with predisposing conditions such as cancer or immunosuppression, acute exacerbation of chronic obstructive pulmonary disease (COPD), bronchitis, macro-aspiration, or MRSA.

Severity	CURB65§	Mortality	Treatment Site	Empiric Therapy∞ (start antibiotics within 4 hours)	Duration of Therapy	Comments
Low	0-1	Less than 3%	Home **OR** Hospitalized for reason other than pneumonia	amoxicillin 500 mg – 1000 mg PO three times daily* **OR** doxycycline 100 mg PO twice daily **OR** Macrolide PO (clarithromycin 500 mg PO twice daily* OR azithromycin 500 mg PO on day one then 250 mg once daily x 4 days)	5 - 7 days	• amoxicillin-clavulanate 875/125 mg PO bid* should be used instead of amoxicillin to provide coverage against Gram-negative bacilli and *S. aureus* when required (e.g., post-influenza, alcoholism, COPD, nursing home) • Amoxicillin is the oral beta-lactam that offers the best coverage against *S. pneumoniae*. Microbiology Tests: None *routinely* (unless hospitalized, see below)
Moderate	2	9%	Hospital	amoxicillin 1000 mg PO three times daily* **+** [macrolide PO or doxycycline 100 mg PO bid] **OR** ampicillin 2 g IV q6h* **+** [macrolide IV (azithromycin 500 mg IV once daily x 3 days) or doxycycline100 mg PO bid] Penicillin Allergy cefuroxime 1.5 g IV q8h **+** [macrolide IV or PO OR doxycycline100 mg PO bid]	7 days	Microbiology Tests: Always order: -Blood cultures (2 sets) -Sputum culture -Urine antigen for pneumococcus and legionellosis‡ (Depending on clinical context, consider investigation for atypical pathogens and viruses)
High	3 or greater	15-40%	Hospital (consider ICU)	cefTRIAXone 2 g IV once daily **+** [macrolide IV or PO OR doxycycline 100 mg PO bid] **OR** levofloxacin 750 mg IV once daily* **+** ampicillin 2 g IV q6h* • For critically ill patients, combinations including doxycycline are not preferred • If legionellosis strongly suspected, consider using levofloxacin • Care with use of levofloxacin: association with *C. difficile* and nosocomial MRSA colonization	7 - 10 days [may extend to 14-21 days according to clinical judgment (e.g. *S. aureus*,)]	

§ CURB65 calculator, 1 point for any of the following:

-Confusion (new)
-Urea (greater than 7 mmol/L)
-Respiration (greater than or equal to 30/min)
-Blood Pressure (less than 90 mm Hg systolic or less than or equal to 60 mm Hg diastolic)
-**A**ge (**65** or greater)

• Interpretation of CURB65 score *in conjunction with clinical judgment*. Too loose an interpretation of "severe pneumonia" contributes to overprescribing third generation cephalosporins and respiratory fluoroquinolones

IV-to-PO Step Down:

Parenteral drug	Suggested oral stepdown
azithromycin	azithromycin or clarithromycin
Cephalosporin (any)	amoxicillin + clavulanic acid
levofloxacin + ampicillin	levofloxacin alone ± amoxicillin
Please note, oral monotherapy vs combined therapy (atypicals) → clinical judgment.	

*Dose adjustment required in renal impairment

‡If antigen is positive for *Legionella*, efforts must be made to obtain sputum and advise laboratory that *Legionella* culture is required. This is important for epidemiological purposes in case of an outbreak.

∞If microbial cause of infection known, treat accordingly

Treatment of Cellulitis/Skin Infection

(NB Provincial Health Authorities Anti-infective Stewardship Committee, May 2014)

Cellulitis/Erysipelas Severity	Preferred Empiric Regimens	Duration of Therapy	Comments
Mild (no signs of systemic toxicity) - assess for clinical evidence of MRSA (e.g. purulent boil with spreading cellulitis, previous MRSA infections or colonization)	cephalexin 500 mg PO four times daily[2] β-lactam allergy: clindamycin 300 - 450 mg PO q6h MRSA Suspected: sulfamethoxazole/trimethoprim 800/160 mg to 1600/320 mg (1 or 2 DS tablets) PO twice daily[2] **OR** doxycycline 100 mg PO twice daily	7-10 days	Work-up: None, unless there is an associated fluctuant pustule that can be drained and sent for culture
Moderate (signs of systemic toxicity: documented fever/hypothermia, tachycardia [HR greater than 100 bpm] and hypotension [SBP less than 90 mm Hg or 20 mm Hg below baseline]) **OR** Progression on oral therapy[1]	ceFAZolin 2 g IV q8h[2] Alternative for outpatient management: (only when ambulatory administration of ceFAZolin is not possible): cefTRIAXone 2 g IV q24h β-lactam allergy: clindamycin 600-900 mg IV q8h MRSA suspected: vancomycin 15 mg/kg IV q12h[2] (adjust based on levels to a trough target of 10-15 mg/L)	Step down as soon as possible to PO (See options in row above), usually total 7-10 days	Work-up: As above plus: Blood cultures (2 sets) CBC, Creatinine, Electrolytes
Severe (sepsis syndrome, Necrotizing Fasciitis [clinical features of NF include systemic toxicity, deep severe pain – more severe than expected for skin findings, violaceous bullae, rapid spread along fascial planes, gas in soft tissues])	piperacillin-tazobactam 3.375 g IV q6h[2] **AND** clindamycin 900 mg IV q8h	Consult with specialists	Work-up: As above plus: urgent surgical assessment for diagnostic biopsy and/or debridement

Clinical pearls:

- These guidelines are for basic skin infections only, any complicating features on history may require alternative management (Specific but not exclusive examples include: immunocompromised patients, diabetic foot infections, cellulitis associated with a surgical site, trauma or animal/human bites)
- Consider looking for predisposing feature (e.g. Tinea pedis) as source of cellulitis

[1]Assessment of clinical response within 48 hours should be based on pain and fever; **mild progression of erythema expected during this timeframe**

[2] Dose adjustment required in renal impairment

Treatment of Adult Urinary Tract Infections

(NB Provincial Health Authorities Anti-infective Stewardship Committee, May 2014)

Indication	Empiric Therapy (Tailor regimen based on urine/blood C&S results)	Duration of Therapy	Comments
Asymptomatic Bacteriuria	Antibiotic therapy only recommended for: -Prophylaxis for urological procedures when mucosal bleeding expected -Treatment in pregnancy (Select antimicrobial therapy according to urine C&S)	Urological procedures: single dose Others: 3 – 7 days	• Asymptomatic bacteriuria with pyuria is not an indication for antimicrobial therapy
Uncomplicated Cystitis (Lower UTI) (Female patients with dysuria, urgency, frequency, or suprapubic pain with no fever or flank pain)	Preferred Regimen: nitrofurantoin monohydrate/macrocrystals 100 mg po twice daily (Not recommended if CrCl less than 40 mL/min; avoid near term (36-42 weeks) due to risk of haemolytic anemia in the new born) Alternative Regimens: amoxicillin/clavulanate 875/125 mg po twice daily[3] **OR** cefuroxime 500 mg po twice daily **OR** sulfamethoxazole/trimethoprim 800/160 mg po twice daily[1,3] (Not recommended in pregnant women) **OR** fosfomycin 3 g po once	5 days 7 days 7 days 3 days One dose	
Acute Uncomplicated Pyelonephritis (Upper UTI) (Signs/Sx: fever, flank pain, costovertebral tenderness, abdominal/pelvic pain, nausea, vomiting with or without signs/sx of lower tract UTI) **OR** **Complicated UTI** (Complicating Factors: structural abnormality, obstruction, recent urogenital procedure, male sex, immunosuppression, poorly controlled diabetes, spinal cord injury, catheterization or Signs/Sx greater than 7 days)	**Systemically Well:** Preferred Regimen: cefixime 400 mg po once daily[3] Alternative Regimens: amoxicillin/clavulanate 875/125 mg po twice daily[3] Additional options if culture confirmed susceptibility: sulfamethoxazole/trimethoprim 800/160 mg po twice daily[1,3] **OR** ciprofloxacin 500 mg po twice daily[1,3] **Systemically Unwell:** cefTRIAXone 1 g IV once daily[2] **OR** ampicillin 2 g IV q6h + gentamicin 5 mg/kg IV once daily[2,3] **OR** piperacillin/tazobactam 3.375 g IV q6h[2,3] (if at risk of MDR organisms) **Pregnant:** cefTRIAXone 1 g IV once daily[2] **OR** ampicillin 2 g IV q6h + gentamicin 5 mg/kg IV once daily[2,3] **OR** piperacillin/tazobactam 3.375 g IV q6h[2,3] (if at risk of MDR organisms)	See Comments 14 days 14 days 14 days	**Acute Uncomplicated Pyelonephritis** • Outpatient management an option if female, not pregnant, no nausea/vomiting, no evidence of dehydration, sepsis or high fever • Treat for 14 days • May treat for 7 days if female, uncomplicated and using ciprofloxacin or sulfamethoxazole/trimethoprim • For treatment using oral β-lactams, consider an initial single intravenous dose of cefTRIAXone 1 g IV and use a 14 day total duration of antimicrobial therapy **Complicated UTI:** • Treat 7 days if prompt response, female and only lower urinary tract infection • Treat 14 days if male, delayed response, structural abnormality, or upper tract symptoms **Catheter-Associated UTI**: • Pyuria not diagnostic, only treat if symptomatic • Catheters frequently colonized, obtain culture through new catheter • Change catheter if in place for greater than 2 weeks & still required

Clinical Pearls:

- Cloudy & foul smelling urine alone is not considered an indication for a urine culture and sensitivity
- Therapy should be adjusted according to culture and sensitivity results
- Blood cultures should be drawn if febrile, septic, signs and symptoms suggestive of pyelonephritis or immunocompromised
- Post-treatment culture not recommended except in case of persistent or recurrent symptoms or pregnancy
- nitrofurantoin and fosfomycin are not appropriate for men, complicated UTI or systemic infections

[1]CAUTION: Significant E.coli resistance (greater than 20%) to fluoroquinolones, sulfamethoxazole/trimethoprim and amoxicillin exist in some areas of the province; check local antibiogram and confirm urine C&S results when available

[2]De-escalate according to urine/blood C&S and switch IV to PO based on conversion criteria

[3]Dose adjustment required in renal impairment

Introduction

The dosing recommendations presented here are for adults with moderate-to-severe infections and are based on published literature, the Clinical & Laboratory Standards Institute's reference dosing for susceptibility interpretation and clinical experience. The recommended doses should only be used as a reference tool. Patient dosing should be individualized and based on pharmacokinetic and clinical evaluation where possible.

Recommendations for renal dose adjustment are made according to estimated creatinine clearance (CrCl) calculated using the Cockroft-Gault equation, which is used in practice. Estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease 4 (MDRD4) equation, commonly reported with most serum creatinine levels, is NOT interchangeable with CrCl calculated using the Cockroft-Gault equation. The two equations may result in different antimicrobial dosing recommendations in up to 20 to 36% of cases with potential clinical significance.[20] Recommendations for renal dose adjustment in the table below are for modifications of the maintenance doses; no adjustments required for loading doses where applicable.

For patients on intermittent hemodialysis (IHD), antimicrobial dosages and administration times may need to be adjusted. If an antimicrobial is significantly removed by hemodialysis (HD) and recommended to be given post-HD then administration of the dose prior to or during HD should be avoided because drug loss could result in subtherapeutic levels post-HD. The dosing schedule should be adjusted on dialysis days so that the scheduled dose is administered **immediately after** dialysis. Other strategies may include supplementary doses administered post-HD to replace the amount of antimicrobial removed during HD or intermittent post-HD administration (ex. ceFAZolin 2 g IV post-HD 3 times weekly). Please consult your local pharmacy department for guidance in patients receiving peritoneal dialysis, continuous veno-venous hemofiltration, continuous veno-venous hemodiafiltration or continuous renal replacement therapy. Dosing adjustment may also be necessary in patients with severe liver impairment.

In critically ill patients (ex: sepsis), antimicrobial pharmacokinetics can be significantly altered and unstable potentially resulting in sub-optimal dosing. A pharmacy consultation could be considered to optimize antimicrobial doses in this patient population.

ADULT ANTIMICROBIAL DOSING TOOL - November 2015

Drug	General Comments	Usual Adult Dose (CrCl greater than or equal to 50 mL/min)	CrCl 30 - 49 mL/min	CrCl 10 - 29 mL/min	CrCl less than 10 mL/min	Intermittent Hemodialysis (IHD)
Penicillins						
amoxicillin (PO)[1,2,3,4,5,6]		500 mg – 1 g q8h		500 mg q12h	500 mg q24h	500 mg q24h; administer dose after dialysis on dialysis days
amoxicillin/clavulanate (PO)[1,2,7] (dose listed as amoxicillin component)	Do not use 875 mg tablets if CrCl <30 mL/min Less diarrhea with 875 mg given q12h vs.500 mg q8h	500 mg q8h 875 mg q12h		500 mg q12h	500 mg q24h	500 mg q24h; administer dose after dialysis on dialysis days
ampicillin (IV)[1,3,5]	Dose 2 g q4h for endocarditis and other deep space infections‡	1 – 2 g q4-6h	1 – 2 g q6-8h	1 – 2 g q8-12h	1 – 2 g q12-24h	1 – 2 g q12-24h; administer dose after dialysis on dialysis days
cloxacillin (PO)[1,5]		500 – 1000 mg q6h				
cloxacillin (IV)[1,2,5]	Dose 2 g q4h for endocarditis and deep space infections‡	1 – 2 g q4-6h				
penicillin G (IV)[1,5]	Dose 4 million units q4h for endocarditis and deep space infections‡	2 – 4 million units q4-6h	75% of usual dose q4h		20 – 50% of usual dose q4h	20 – 50% of usual dose q4h; administer dose after dialysis on dialysis days
penicillin V (PO)[2,5,8,9]		300 – 600 mg q6h			300 – 600 mg q8h	
piperacillin/tazobactam (IV)[1,2,3,5] (dose listed as piperacillin plus tazobactam components)		3.375 g q6h	2.25 g q6h (CrCl 20 – 40 mL/min)		2.25 g q8h (CrCl less than 20 mL/min)	2.25 g q12h; administer supplementary dose of 0.75 g
	Hospital acquired pneumonia, febrile neutropenia and Pseudomonas spp infections	4.5 g q6h	3.375 g q6h (CrCl 20 – 40 mL/min)		2.25 g q6h (CrCl less than 20 mL/min)	2.25 g q8h; administer supplementary dose of 0.75 g
piperacillin (IV)[1,3,5]		3 – 4 g q6h	3 – 4 g q8h (CrCl 20-40mL/min)	3 – 4 g q12h (CrCl less than 20 mL/min)		2 g q8h; administer supplementary dose of 1 g after dialysis session
Cephalosporins						
ceFAZolin (1st) (IV)[1,5,19]		2 g q8h		2 g q12h	1 – 2 g q24h	1 – 2 g q24h; administer dose after dialysis on dialysis days OR 2 g after dialysis three times weekly if receiving dialysis three times weekly
cephalexin (1st) (PO)[1,3,5]		500 mg – 1 g q6h	500 mg q8h	500 mg q12h	500 mg q12-24h	500 mg q12-24h; administer dose after dialysis on dialysis days
cefadroxil£ (1st) (PO)[1,3,5]	Dose 1 g twice daily for complicated UTI	500 mg – 1 g q12h		500 mg – 1 g q24h	500 mg q24h	500 mg – 1 g three times weekly after dialysis if receiving dialysis three times weekly

(continued on next page)

ADULT ANTIMICROBIAL DOSING TOOL - November 2015

Drug	General Comments	Usual Adult Dose (CrCl greater than or equal to 50 mL/min)	CrCl 30 - 49 mL/min	CrCl 10 - 29 mL/min	CrCl less than 10 mL/min	Intermittent Hemodialysis (IHD)
cefaclor[£] (2nd) (PO)[1,3,5]		250 - 500 mg q8h			250 mg q8h	250 mg q8h ; administer supplementary dose of 250 mg after dialysis session
cefuroxime axetil (2nd) (PO)[1,2,3,5]		500 mg q12h			250 – 500 mg q24h	250 – 500 mg q24h; administer dose after dialysis on dialysis days
cefuroxime (2nd) (IV)[1,2,5]		1.5 g q8h (CrCl greater than 20 mL/min)		1.5 g q12h (CrCl 10-19 mL/min)	1.5 g q24h	1.5 g q24h; administer dose after dialysis on dialysis days
cefOXitin (2nd) (IV)[1,5,10]	Dose 2 g q6h for moderate to severe infections such as intra-abdominal infections	1 – 2 g q6-8h	1 – 2 g q8h	1 – 2 g q12h	1 – 2 g q24h	1 – 2 g q24h; administer dose after dialysis on dialysis days
cefprozil (2nd) (PO)[1,3,5]		500 mg q12h		250 mg q12h		250 mg q12h; administer supplementary dose of 250 mg after dialysis session
cefixime (3rd) (PO)[2,3]		400 mg q24h			200 mg q24h	200 mg q24h
cefTRIAXone (3rd) (IV)[1]	Dose 2 g q12h for CNS infections or *Enterococcus faecalis* endocarditis in combination with ampicillin	1 – 2 g q24h				
cefotaxime (3rd) (IV)[1,2,3]	Moderate to severe infection	1 – 2 g q6-8h		1 – 2 g q12h	1 – 2 g q24h	1 – 2 g q24h; administer dose after dialysis on dialysis days
	CNS infection	2 g q4h	2 g q6h	2 g q8h	2 g q12h	2 g q12-24h; administer dose after dialysis on dialysis days
cefTAZidime (3rd) (IV)[1,3,5]		2 g 8h	2 g q12h	2 g q24h	1 g q24h	1 g q24h; administer dose after dialysis on dialysis days OR 2 g after dialysis three times weekly if receiving dialysis three times weekly
cefepime[£] (4th) (IV)[1,2]	Uncomplicated mild to moderate infections	1 – 2 g q8-12h	1 – 2 g q12 – 24h	1 – 2 g q24h	1 g q24h	1g q24h; administer dose after dialysis on dialysis days OR 2 g after dialysis three times weekly if receiving dialysis three times weekly
	Severe infections including febrile neutropenia, hospital acquire pneumonia deep space infections‡ or coverage for *Pseudomonas aeruginosa*	2 g q8h	2 g q12h	2 g q24h		

(continued on next page)

ADULT ANTIMICROBIAL DOSING TOOL - November 2015

Drug	General Comments	Usual Adult Dose (CrCl greater than or equal to 50 mL/min)	CrCl 30 - 49 mL/min	CrCl 10 - 29 mL/min	CrCl less than 10 mL/min	Intermittent Hemodialysis (IHD)
Carbapenems						
ertapenem[£] (IV/IM)[13,5]		1 g q24h		500 mg q24h		500 mg q24h; administer supplementary dose of 150 mg after dialysis session if daily dose given less than 6 hr before start of HD
imipenem/cilastatin[R] (IV)[1,11]	Meropenem preferred for CNS infections and when CrCl less than 30 mL/min	500 – 1000 mg q6h	500 mg q6-8h (CrCl 31 – 70 mL/min)	500 mg q8-12h (CrCl 21 – 30 mL/min) **[consider meropenem]**	250 – 500 mg q12h (CrCl 0 – 20 mL/min) **[consider meropenem]**	250 – 500 mg q12h; administer dose after dialysis on dialysis days **[consider meropenem]**
meropenem[R] (IV)[1,2,3,5]	q6h dosing regimen: Caution: do NOT use this regimen for CNS infections	500 mg q6h	500 mg q8h (CrCl 26 – 50 mL/min)	500 mg q12h (CrCl 10 – 25 mL/min)	500 mg q24h	500 mg q24h; administer dose after dialysis on dialysis days
	q8h dosing regimen: Dose 2 g q8h for CNS infections	1 – 2 g q8h	1 – 2 g q12h		500 mg – 1000 mg q24h	500 mg – 1000 mg q24h; administer dose after dialysis on dialysis days
Aminoglycosides – Adjust dose for serum drug levels where applicable. For prolonged therapies consider pharmacy consult for appropriate dosing and monitoring						
gentamicin/tobramycin (IV) Extended Interval Dosing[2,4,14]	7 mg/kg for serious infections Dosing based on IBW, unless actual body weight greater than 20% above IBW, then use dosing weight	5 – 7 mg/kg q24h (CrCl greater than or equal to 60 mL/min)	5 – 7 mg/kg q36h (CrCl 40 – 59 mL/min)	5 – 7 mg/kg q48h (CrCl 20 – 39 mL/min) OR Consider conventional dosing	5 – 7 mg/kg IV to start then use serial serum drug levels to adjust (CrCl less than 20 mL/min) OR Consider conventional dosing	1.5 – 2 mg/kg loading dose followed by 1 mg/kg maintenance dose at the end of each dialysis session; dose adjustments based on pre-dialysis levels (dosing based on patient's dry weight if not obese; if dry weight is greater than 20% of IBW then dose is based off patients dosing weight)
gentamicin/tobramycin (IV) Conventional Dosing [2,4,14]	Dosing based on IBW, unless actual body weight greater than 20% above IBW, then use dosing weight Consider a loading dose of 2 mg/kg to start	1.5 – 2 mg/kg q8h (CrCl greater than or equal to 80 mL/min) 1.5 – 2 mg/kg q12h (CrCl 50 – 79 mL/min)	1.5 – 2 mg/kg q24h (CrCl 20 – 49 mL/min)	1.5 – 2 mg/kg q48-72hrs OR use serial drug levels to adjust; close monitoring recommended (CrCl less than 20 mL/min)		
gentamicin/tobramycin (IV) Synergy Dosing[2,3,14] (for Gram positive infections only; tobramycin not for synergy against Enterococcus spp infections)	Dosing based on IBW, unless actual body weight greater than 20% above IBW, then use dosing weight	1 mg/kg q8h (CrCl greater than or equal to 80 mL/min) 1 mg/kg q12h (CrCl 50 – 79 mL/min)	1 mg/kg q24h (CrCl 20 – 49 mL/min)	1 mg/kg q48-72hrs OR use serial drug levels to adjust; close monitoring recommended (CrCl less than 20 mL/min)		1 mg/kg at the end of each dialysis session; dose adjustments based on pre-dialysis levels (dosing based on patient's dry weight if not obese; if dry weight is greater than 20% of IBW then dose is based off patients dosing weight)

(continued on next page)

ADULT ANTIMICROBIAL DOSING TOOL - November 2015

Drug	General Comments	Usual Adult Dose (CrCl greater than or equal to 50 mL/min)	CrCl 30 - 49 mL/min	CrCl 10 - 29 mL/min	CrCl less than 10 mL/min	Intermittent Hemodialysis (IHD)
amikacin (IV) Extended Interval Dosing[1,2,4]	Dosing based on IBW, unless actual body weight greater than 20% above IBW, then use dosing weight	15 mg/kg q24h (CrCl greater than or equal to 60 mL/min)	15 mg/kg q36h (CrCl 40 – 59 mL/min)	15 mg/kg q48h (CrCl 20 – 39 mL/min) OR Consider conventional dosing	15 mg/kg to start then use serial serum drug levels to adjust (CrCl less than 20 mL/min) OR Consider conventional dosing	5 – 7.5 mg/kg at the end of each dialysis session; dose adjustments based on pre-dialysis levels (dosing based on patient's dry weight if not obese; if dry weight is greater than 20% of IBW then dose is based off patients dosing weight)
amikacin (IV) Conventional Dosing[1,2,4]	Dosing based on IBW, unless actual body weight greater than 20% above IBW, then use dosing weight Consider a loading dose of 7.5 mg/kg to start	5 – 7.5 mg/kg q8h (CrCl greater than or equal to 80 mL/min) 5 – 7.5 mg/kg q12h (CrCl 50 – 79 mL/min)	5 – 7.5 mg/kg q24h (CrCl 20 – 49 mL/min)	5 – 7.5 mg/kg q48-72hrs OR use serial serum drug levels to adjust; close monitoring recommended (CrCl less than 20 mL/min)		
Macrolides						
erythromycin (IV)[1,2]		500 – 1000 mg q6h			50 – 75% dose q6h	
erythromycin (PO)[1,2,3]	Formulary products: •erythromycin base 250 mg capsules containing EC pellets •erythromycin estolate 50 mg/mL suspension	250 – 500 mg q6h			50 – 75% dose q6h	
azithromycin (IV)[1]		500 mg q24h x 3-5 days			Use with caution – No dose adjustment provided	
azithromycin (PO)[1]		500 mg q24h x 3 days OR 500 mg on day one, then 250 mg daily for days 2 to 5				
clarithromycin (PO)[1,3,4]		500 mg q12h		500 mg q24h		500 mg q24h; administer dose after dialysis on dialysis days
clarithromycin XL[£] (PO)[1,3]		1000 mg q24h		500 mg q24h		500 mg q24h; administer dose after dialysis on dialysis days
Quinolones						
ciprofloxacin (IV)[1,2,8]	Uncomplicated UTI: 400 mg q24h	400 mg q12h		400 mg q24h		400 mg q24h; administer dose after dialysis on dialysis days
	Severe infections; infections due to *Pseudomonas aeruginosa*	400 mg q8h	400 mg q12h			

(continued on next page)

ADULT ANTIMICROBIAL DOSING TOOL - November 2015

Drug	General Comments	Usual Adult Dose (CrCl greater than or equal to 50 mL/min)	CrCl 30 - 49 mL/min	CrCl 10 - 29 mL/min	CrCl less than 10 mL/min	Intermittent Hemodialysis (IHD)
ciprofloxacin (PO)[1,2,9]	UTI (uncomplicated): 250 mg q12h	500 mg q12h		500 mg q24h		250 – 500 mg q24h; administer dose after dialysis on dialysis days
	Infection of the bone or skin, infections due to *Pseudomonas spp* or severe infections: 750 mg q12h	750 mg q12h	500 mg q12h			
levofloxacin (PO/IV)[1]		500 mg q24h	500 mg once then 250 mg q24h (CrCl 20 – 49 mL/min)	500 mg once then 250 mg q48h (CrCl less than 20 mL/min or IHD)		
	High dose for bacteremia, complicated UTI, pyelonephritis, complicated skin infection, nosocomial pneumonia, intra-abdominal infections, infections due to *Pseudomonas spp*	750 mg q24h	750 mg q48h (CrCl 20 – 49 mL/min)	750 mg once then 500 mg q48h (CrCl less than 20 mL/min or IHD)		
moxifloxacin(PO/IV)[1]		400 mg q24h				
norfloxacin[£] (PO)[1,3]		400 mg q12h		400 mg q24h		
Tetracyclines						
doxycycline (PO)[1]		100 mg q12h				
minocycline[£] (PO)[1,3,5]		200 mg then 100 mg q12h	Usual dose (Doxycycline preferred)			
tetracycline (PO)[1,3,5]		250 – 500 mg q6h 250 – 500 mg q8-12h (CrCl 50 to 80 mL/min)	250 – 500 mg q12 – 24h (Doxycycline preferred)	250 – 500 mg q24h (Doxycycline preferred)		Use not recommended
tigecycline[R] (IV)[1]		100 mg initially, then 50 mg q12h				
Other						
clindamycin (IV)[1]		600 – 900 mg q8h				
clindamycin (PO)[1,12]		300 – 450 mg q6-8h				
DAPTOmycin[R] (IV)[1,3]	Skin and soft tissue infections: 4 mg/kg q24h Severe infections: 8-10 mg/kg q24h Monitor baseline and weekly creatine kinase levels	6 – 8 mg/kg q24h		Usual dose q48h if CrCl less than 30 mL/min		Administer dose after dialysis on dialysis days

(continued on next page)

ADULT ANTIMICROBIAL DOSING TOOL - November 2015

Drug	General Comments	Usual Adult Dose (CrCl greater than or equal to 50 mL/min)	CrCl 30 - 49 mL/min	CrCl 10 - 29 mL/min	CrCl less than 10 mL/min	Intermittent Hemodialysis (IHD)
fosfomycin (PO)	Uncomplicated UTI	3 g ONCE				
linezolid[R] (PO/IV)[1,2,3]		600 mg q12h				Administer dose after dialysis on dialysis days
metroNIDAZOLE (PO/IV)[1,2]	Dose 500 mg q8h for Clostridium difficile infection or CNS infection	500 mg q12h				Consider a supplemental dose after dialysis if administration cannot be separated from the dialysis session
nitrofurantoin monohydrate/macrocrystal sustained release capsules (MACROBID) (PO)[1]		100 mg q12h	Contraindicated if CrCl less than 40 mL/min			
nitrofurantoin regular release oral solid[R,1]		50 – 100 mg q6h				
sulfamethoxazole + trimethoprim (IV) •Each mL of injectable contains sulfamethoxazole 80 mg and trimethoprim 16 mg[1,2,8]	Dose listed as trimethoprim (TMP) component Use of sulfamethoxazole + trimethoprim in moderate to severe renal dysfunction has not been not adequately studied, close monitoring of patient response, electrolytes and serum creatinine recommended	8 – 20 mg TMP/kg/day divided q6-12h **Pneumocystis jiroveci Treatment:** 15 – 20 mg/kg/day divided q6-8h	50% of usual dose (CrCl 15 – 30 mL/min) ***Pneumocystis jiroveci* Treatment (CrCl 15 – 30 mL/min):** 15 – 20 mg/kg/day divided q6-8h for 48 hr then 7 – 10 mg/kg/day divided q12h	Generally not recommended, but if required: 4 – 6 mg/kg/day divided q12-24h (CrCl less than 15 mL/min) ***Pneumocystis jiroveci* Treatment (CrCl less than15 mL/min):** 7 – 10 mg/kg/day divided q12-24h	2.5 – 10 mg/kg trimethoprim q24h; administer dose after dialysis on dialysis days OR 5 – 20 mg/kg 3 times weekly after dialysis if receiving dialysis three times weekly ***Pneumocystis jiroveci* Treatment:** 7 – 10 mg/kg after dialysis three times weekly if receiving dialysis three times weekly
sulfamethoxazole + trimethoprim (PO) •Each regular strength tablet contains sulfamethoxazole 400 mg and trimethoprim 80 mg •Each mL of oral suspension contains sulfamethoxazole 40 mg and trimethoprim 8 mg[1,2,8]		sulfamethoxazole/trimethoprim 800/160 to 1600/320 mg q12h **Pneumocystis jiroveci Treatment**: 15 – 20 mg/kg/day divided q6-8h				
trimethoprim (PO)[2]		100 mg q12h	50 mg q12h (CrCl 15 – 30 mL/min)	Generally not recommended if CrCl less than 15 mL/min, but if required: 50 mg q24h		Administer dose after dialysis on dialysis days

(continued on next page)

ADULT ANTIMICROBIAL DOSING TOOL - November 2015

Drug	General Comments	Usual Adult Dose (CrCl greater than or equal to 50 mL/min)	CrCl 30 - 49 mL/min	CrCl 10 - 29 mL/min	CrCl less than 10 mL/min	Intermittent Hemodialysis (IHD)
vancomycin (IV)[2,8,13]	Consider a loading dose of 25-30 mg/kg if severe infection, adjusting maintenance doses based on renal function Dosing based on actual body weight Maximum of 2 g per dose for maintenance doses Adjust dose for serum drug levels where applicable. For prolonged therapies consider pharmacy consult for appropriate dosing and monitoring	**Target Trough 10 – 20 mg/L** 15 mg/kg q12h (CrCl greater than 80 mL/min) 15 mg/kg q24h (CrCl 40 – 80 mL/min)	**Target Trough 10 – 20 mg/L** 15 mg/kg q36h (CrCl 20 – 40 mL/min)	**Target Trough 10 – 20 mg/L** 15 mg/kg q48h (CrCl 10 – 20 mL/min)	Consider loading dose of 25 – 30 mg/kg; then use serial serum drug levels to adjust	Less than 70 kg: 1000 mg loading dose then 500 mg maintenance dose infused after dialysis; 70-100 kg: 1250 mg loading dose then 750 mg maintenance dose infused after dialysis; Greater than 100 kg: 1500 mg loading dose then 1000 mg maintenance dose infused after dialysis (Adjust maintenance doses based on pre-dialysis vancomycin trough levels)
		Target Trough 15 – 20 mg/L 15 mg/kg q8h (CrCl greater than 80 mL/min) 15 mg/kg q12h (CrCl 40 – 80 mL/min)	**Target Trough 15 – 20 mg/L** 15 mg/kg q24h (CrCl 20 – 40 mL/min)	**Target Trough 15 – 20 mg/L** 15 mg/kg q48h (CrCl 10 – 20 mL/min)		
vancomycin (PO)[1]	*C. difficile* infection **ONLY** See NB-ASC *Clostridium difficile* Infection treatment guidelines for more details	125 – 500 mg q6h				
Antivirals						
acyclovir (IV)[1,2,3,9]	Dose based on ideal or dosing body weight Herpes zoster (shingles)/ Herpes simplex/ Varicella-zoster (chickenpox) in an immunocompromised host or patient with severe disease or encephalitis: 10 - 15 mg/kg q8h	5 – 10 mg/kg q8h	5 – 10 mg/kg q12h (CrCl 25 – 50 mL/min)	5 – 10 mg/kg q24h (CrCl 10 – 25 mL/min)	2.5 – 5 mg/kg q24h	Administer after dialysis on dialysis days
acyclovir (PO)[1]	Herpes Zoster, and Varicella: 800 mg five times a day	400 – 800 mg q8h to five times a day		400 – 800 mg q8h	200 – 800 mg q12h	Administer dose after dialysis on dialysis days
famciclovir[£] (PO)[1,2,3,8]	Herpes zoster (shingles)	500 mg q8h	500 mg q12h (CrCl 40 – 59 mL/min)	500 mg q24h (CrCl 20 – 39 mL/min)	250 mg q24h (CrCl less than 20 mL/min)	250 mg after each dialysis session
	Primary genital herpes	250 mg q8h (CrCl greater than 40 mL/min)	250 mg q12h (CrCl 20 – 39 mL/min)		250 mg q24h (CrCl less than 20 mL/min)	250 mg after each dialysis session
	Recurrent Genital herpes	1000 mg q12h x 1 day	500 mg q12h x 1 day (CrCl 40 – 59 mL/min)	500 mg as a single dose (CrCl 20 – 39 mL/min)	250 mg as a single dose after a dialysis session (CrCl <20 mL/min)	

(continued on next page)

ADULT ANTIMICROBIAL DOSING TOOL - November 2015

Drug	General Comments	Usual Adult Dose (CrCl greater than or equal to 50 mL/min)	CrCl 30 - 49 mL/min	CrCl 10 - 29 mL/min	CrCl less than 10 mL/min	Intermittent Hemodialysis (IHD)
ganciclovir (IV)[1,8]	Induction	5 mg/kg q12h or 2.5 mg/kg q12h if (CrCl 50 – 69 mL/min)	2.5 mg/kg q24h	1.25 mg/kg q24h	1.25 mg/kg 3 times weekly (following dialysis, if receiving dialysis three times weekly)	
	Maintenance	5 mg/kg q24h or 2.5 mg/kg q24 h if (CrCl 50 – 69 mL/min)	1.25 mg/kg q24h	0.625 mg/kg q24h	0.625 mg/kg three times weekly (following dialysis, if receiving dialysis three times weekly)	
oseltamivir (PO)[1,2,15]	Treatment (for 5 days)	75 mg q12h (CrCl greater than 60 mL/min)	30 mg q12h (CrCl 30 – 60 mL/min)	30 mg q24h	Use with caution: 75 mg ONCE	75 mg after each dialysis session
	Prophylaxis (for 10 to 14 days)	75 mg q24h	30 mg q24h (CrCl 30 – 60 mL/min)	30 mg q2days	Use with caution: 30 mg ONCE	An initial 30 mg dose may be given prior to HD if exposed during the 48 hours between dialysis sessions. Then administer 30 mg after alternate dialysis sessions
valACYclovir (PO)[1,2,16]	Herpes zoster (shingles)	1 g q8h	1 g q12h	1 g q24h	500 mg q24h	1 g three times weekly after dialysis, if receiving dialysis three times weekly
	Herpes labialis	2g q12h x 2 doses	1 g q12h x 2 doses	500 mg q12h x 2 doses	500 mg as a single dose	Administer dose after a dialysis session
	Primary genital herpes	1g q12h		1g q24h	500 mg q24h	Administer dose after dialysis on dialysis days
	Recurrent genital herpes	500 mg q12h or 1g q24h x 3 days		500 mg q24h		Administer dose after dialysis on dialysis days
	Herpes simplex/ Varicella zoster Treatment in oncology patients	1 g q8h	1 g q12h	1 g q24h	500 mg q24h	1 g three times weekly after dialysis, if receiving dialysis three times weekly
	Herpes simplex/ Varicella zoster prophylaxis in oncology patients	500 mg q8-12h		500 mg q12h	500 mg q24h	Administer dose after dialysis on dialysis days
valGANciclovir (PO)[1,2,8]	Induction	900 mg q12h (CrCl greater than or equal to 60 mL/min)	450 mg q12h (CrCl 40 – 59 mL/min) 450 mg q24h (CrCl 25 – 39 mL/min)	450 mg q2days (CrCl 10 – 24 ml/min)	Consider ID or Transplant Consult	
	Maintenance	900 mg q24h (CrCl greater than or equal to 60 mL/min)	450 mg q24h (CrCl 40 – 59 mL/min) 450 mg q2days (CrCl 25-39 mL/min)	450 mg 2x/week (CrCl 10 – 24 ml/min)	Consider ID or Transplant Consult	

(continued on next page)

ADULT ANTIMICROBIAL DOSING TOOL - November 2015

Drug	General Comments	Usual Adult Dose (CrCl greater than or equal to 50 mL/min)	CrCl 30 - 49 mL/min	CrCl 10 - 29 mL/min	CrCl less than 10 mL/min	Intermittent Hemodialysis (IHD)
zanamivir£ (inhaled)[1,15]	Treatment	10 mg inhaled orally q12h				
	Prophylaxis	10 mg inhaled orally q24h				
Antifungals						
amphotericin B (IV)[1,2,4,8] FUNGIZONE		0.5-1 mg/kg q24h				
amphotericin B, lipid complex (IV)[1,4,8] ABELCET		5 mg/kg q24h				
amphotericin B, liposomal£ (IV)[1,8] AMBISOME		3 – 6 mg/kg q24h				
anidulafungin£ (IV)[1]		200 mg once then 100 mg q24h				
caspofungin£ (IV)[1]		70 mg once, then 50 mg q24h				
micafungin (IV)[1,17]		100 mg q24h				
	Esophageal candidiasis OR invasive aspergillosis	150 mg q24h				
fluconazole (PO/IV)[1]	Candidemia: 800 mg loading dose on day 1 then 400 mg daily	400 – 800 mg q24h	50% of the dose if CrCl 50 mL/min or less			Administer usual dose after dialysis on dialysis days; on non-dialysis days, reduce dose by 50 %
itraconazole (PO)[1]	Capsules and oral solution NOT bioequivalent Aspergillosis: Consider loading dose of 200 mg q8h x 3 days; then 200 mg q12h	100 – 200 mg q24h				
posaconazole (IV)[1,8,9]		Loading dose, 300 mg IV infusion q12h on day 1, followed by 300 mg IV infusion q24h starting on day 2	Accumulation & resultant toxicity of the diluent can occur if CrCl less than 50 mL/min.			
posaconazole (PO)[1,8,9] **Delayed release tablet and oral suspension are NOT bioequivalent	Delayed-Release Tablet	Loading dose of 300 mg q12h on day 1 followed by 300 mg q24h starting on day 2				
	Oral Suspension	Prophylaxis: 200 mg three times daily Treatment of invasive fungal infections: 400 mg q12h or 200 mg four times daily for patients unable to tolerate a meal or nutritional supplement				
voriconazole (IV)[1]	Therapeutic drug monitoring may be considered	6 mg/kg q12h x 2 doses then 4 mg/kg q12h thereafter	Accumulation & resultant toxicity of the diluent can occur if CrCl less than 50 mL/min. Use oral voriconazole at normal doses			

(continued on next page)

ADULT ANTIMICROBIAL DOSING TOOL - November 2015

Drug	General Comments	Usual Adult Dose (CrCl greater than or equal to 50 mL/min)	CrCl 30 - 49 mL/min	CrCl 10 - 29 mL/min	CrCl less than 10 mL/min	Intermittent Hemodialysis (IHD)
voriconazole (PO)[1,18]	Therapeutic drug monitoring may be considered	400 mg q12h x 2 doses then 200 mg q12h for patients weighing greater than or equal to 40 kg; OR 200 mg q12h x 2 doses then 100 mg q12h for patients less than 40 kg IDSA recommendations for invasive aspergillosis: may consider oral therapy in place of IV with dosing of 4 mg/kg rounded up to convenient tablet dosage form every 12 hours. IV administration preferred in serious infections as comparative efficacy with the oral route has not been established.				

Legend:
R: restricted antimicrobial
£: antimicrobial *not* listed on NB Hospital Formulary
‡: deep space infections include meningitis, septic arthritis,complicated abscesses, etc
IBW: ideal body weight
Dry body weight **in hemodialysis**: defined as the lowest tolerated post-dialysis weight at which there are minimal signs or symptoms of hypovolemia or hypervolemia.[21]
Obesity: defined as an actual body weight greater than 20% above patient's calculated ideal body weight.

Cockcroft-Gault equation for estimated creatinine clearance (mL/min):

$$\text{CrCL (females)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{\text{serum creatinine (mcmol/L)}}*$$

CrCl (males) = CrCl (females) x 1.2

*For weight, use ideal body weight *unless* actual body weight is greater than 20% of ideal body weight, in which case use dosing body weight.

Ideal body weight (IBW):
IBW (females) = 45.5 kg + 0.92 x (height in cm – 150 cm) ***OR*** 45.5 kg + 2.3 × (height in inches – 60 inches)
IBW (males) = 50 kg + 0.92 x (height in cm – 150 cm) ***OR*** 50 kg + 2.3 × (height in inches – 60 inches)

Dosing weight (kg) = IBW + 0.4 × (actual body weight – IBW)

References:

1. Lexi-Comp Drug Information: (See specific drug monograph) Accessed online May 2015
2. Blondel-Hill E and Fryters S. Bugs and Drugs An Antimicrobial/Infectious Diseases Reference 2012
3. The Johns Hopkins POC-IT ABX Guide The Unbound Plateform: (See Specific drug monograph) Accessed online May 2015
4. Antimicrobial Handbook – 2012. Editor: Dr Kathy Slayter. Antimicrobial Agents Subcommittee. Capital Health, Nova Scotia.
5. Aronoff GR, Bennett WM, Berns JS, Brier ME, Kasbekar N *et al.* Drug Prescribing in Renal Failure Dosing Guidelines for Adults and Childeren. 5th Ed. American College of Physicians Philadelphia 2007
6. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD *et al.* Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. Clinical Infectious Diseases 2007; 44:S27-72
7. RxFiles Drug Comparison Charts. 10th Ed. October 2014
8. DrugDex: (See specific product monograph). Accessed online May 2015
9. e-CPS Drug Monographs:(see specific drug monograph). Accessed online May 2015
10. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJC *et al.* Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clinical Infectious Diseases 2010;50:133-164
11. Parenteral Drug Therapy Manual. Horizon Health Network – Moncton Area. Accessed online May 2015
12. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ *et al.* Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America. Clinical Infectious Diseases http://www.idsociety.org/Organ_System/#Skin & Soft Tissue Accessed online May 2015
13. Rybak M, Lomaestro B, Rotschafer JC, Moellering R Jr., Craig W *et al.* Therapeutic drug monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health-Syst Pharm. 2009; 66:82-98
14. Horizon Health Network Standard Operating Practice Nephrology & Hypertension Services, Hemodialysis. Vancomycin and Aminoglycoside Dosing and Monitoring Guidelines. Effective date: 03/02/2012
15. Stiver HG, Evans GA, Aoki FY, Allen UD and Laverdiere M. Guidance on the use of antiviral drugs for influenza in acute care facilities in Canada, 2014-2015. Ca J Infect Dis Med Microbiol 26(1):e5-e8
16. NCCN Clinical Practice Guidelines in Oncology Prevention and Treatment of Cancer Related Infections Version 2.2015. http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf Accessed online May 2015
17. Enoch DA, Idris SF, Aliyu SH, Micallef C, Sule O and Karas JA. Micafungin for the treatment of invasive aspergillosis. Journal of Infection 2014 68;507-526
18. Walsh TJ, Anaissie EJ, Denning DW, Herbrecht R, Kontoyiannis DP *et al.* Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Diseases Society of America. Clinical Infectious Diseases 2008;46:327-60
19. Turnidge, JD. Cefazolin and Enterobacteriaceae: Rationale for Revised Susceptibility Testing Breakpoints. Clinical Infectious Diseases 2011;52(7):917-924
20. Wargo KA, Eiland EH, Hamm W, English TM and Phillippe HM. Comparison of the Modification of Diet in Renal Disease and Cockcroft-Gault Equations for Antimicrobial Dosage Adjustments. Ann Pharmacother 2006; 40:1248-1253.
21. Agarwal R and Weir MR. Dry Weight: A Concept Revisited in an Effort to Avoid Medication-Directed Approaches for Blood Pressure Control in Hemodialysis Patients. Clin J Am Soc Nephrol. 2010 Jul;5(7):1255-1260

Management of Penicillin and Beta-Lactam Allergy

(NB Provincial Health Authorities Anti-Infective Stewardship Committee, February 2016)

Key Points

- Beta-lactams are generally safe; allergic and adverse drug reactions are over diagnosed and reported
- Nonpruritic, nonurticarial rashes occur in up to 10% of patients receiving penicillins. These rashes are usually not allergic and are not a contraindication to the use of a different beta-lactam
- The frequently cited risk of 8 to 10% cross-reactivity between penicillins and cephalosporins is an overestimate based on studies from the 1970's that are now considered flawed
- Expect new intolerances (i.e. any allergy or adverse reaction reported in a drug allergy field) to be reported after 0.5 to 4% of all antimicrobial courses depending on the gender and specific antimicrobial. Expect a higher incidence of new intolerances in patients with three or more prior medication intolerances.[1]
- For type-1 immediate hypersensitivity reactions (IgE-mediated), cross-reactivity among penicillins (table 1) is expected due to similar core structure and/or major/minor antigenic determinants, use not recommended without desensitization.
- For type-1 immediate hypersensitivity reactions, cross-reactivity between penicillins (table 1) and cephalosporins is due to similarities in the side chains; risk of cross-reactivity will only be significant between penicillins and cephalosporins with similar side chains
- Only type-1 immediate hypersensitivity to a penicillin manifesting as anaphylaxis, bronchospasm, angioedema, hypotension, urticaria or pruritic rash warrant the avoidance of cephalosporins with similar side chains and other penicillins
- Patients with type-1 immediate hypersensitivity to a penicillin may be safely given cephalosporins with side chains unrelated to the offending agent (**See figure 1 & 2 below**)
  - For example, ceFAZolin does not share a side chain with any beta-lactam and is not expected to cross react with other agents
- Cross-reactivity between cephalosporins is low due to the heterogeneity between side chains; therefore, a patient with a cephalosporin allergy may be prescribed another cephalosporin with a dissimilar side chain
- Cross-reactivity between penicillins and carbapenems is low. Carbapenems would be a reasonable option when antibiotics are required in patients with type-1 immediate hypersensitivity reaction to penicillins
- Patients with reported Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, immune hepatitis, hemolytic anemia, serum sickness or interstitial nephritis secondary to beta-lactam use should avoid beta-lactams and not receive beta-lactam skin testing, re-challenging or desensitization
- Penicillin skin tests can be used to predict penicillin sensitivity and have a 97-99% negative predictive value
- Any patient with possibility of type-1 immediate hypersensitivity to a beta-lactam should be referred for allergy confirmation

Management of the Beta-Lactam Allergy (Figure 1 & Figure 2) [1,2,3,4]

1. Avoid the unnecessary use of antimicrobials, particularly in the setting of viral infections.
2. Complete a thorough investigation of the patient's allergies, including, but not limited to: the specific drug the patient received, a detailed description of the reaction, temporal relationship of the onset of the reaction with respect to when the drug was given, concomitant drugs received when the reaction occurred, the time elapsed since the reaction occurred and tolerability of any structurally related compounds
   a. Patient reports intolerance (e.g. nausea, vomiting, diarrhea, headache) – likely not allergic, attempt beta-lactam therapy
   b. Patient has a documented severe non-IgE mediated hypersensitivity reaction to a beta-lactam (e.g. interstitial nephritis, immune hepatitis, hemolytic anemia, serum sickness, severe cutaneous reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), etc…) – avoid all beta-lactam antibiotics including their use for allergy testing, desensitization and re-challenge.
      - Treatment options include non-beta-lactam antibiotics
   c. Patient has a documented severe type-1 immediate hypersensitivity reaction to a penicillin (e.g. anaphylaxis, urticaria, angioedema, hypotension, bronchospasm, stridor, pruritis) – avoid other penicillins and cephalosporins with similar side chain, unless patient undergoes desensitization.
      - Treatment options include cephalosporins with dissimilar side chains or carbapenems or non-beta-lactam antibiotics – Note: ceFAZolin does not share a side chain with any beta-lactam agent.
   d. Patient has a documented severe type-1 immediate hypersensitivity reaction to a cephalosporin (e.g. anaphylaxis, urticaria, angioedema, hypotension, bronchospasm, stridor, pruritis) – avoid cephalosporins with similar side chains and penicillins with similar side chains (see figure 2) unless desensitization is performed.
      - Treatment options include penicillins with dissimilar side chains, cephalosporins with dissimilar side chains, carbapenems or non-beta-lactam antibiotics.

Figure 1: Management Diagram

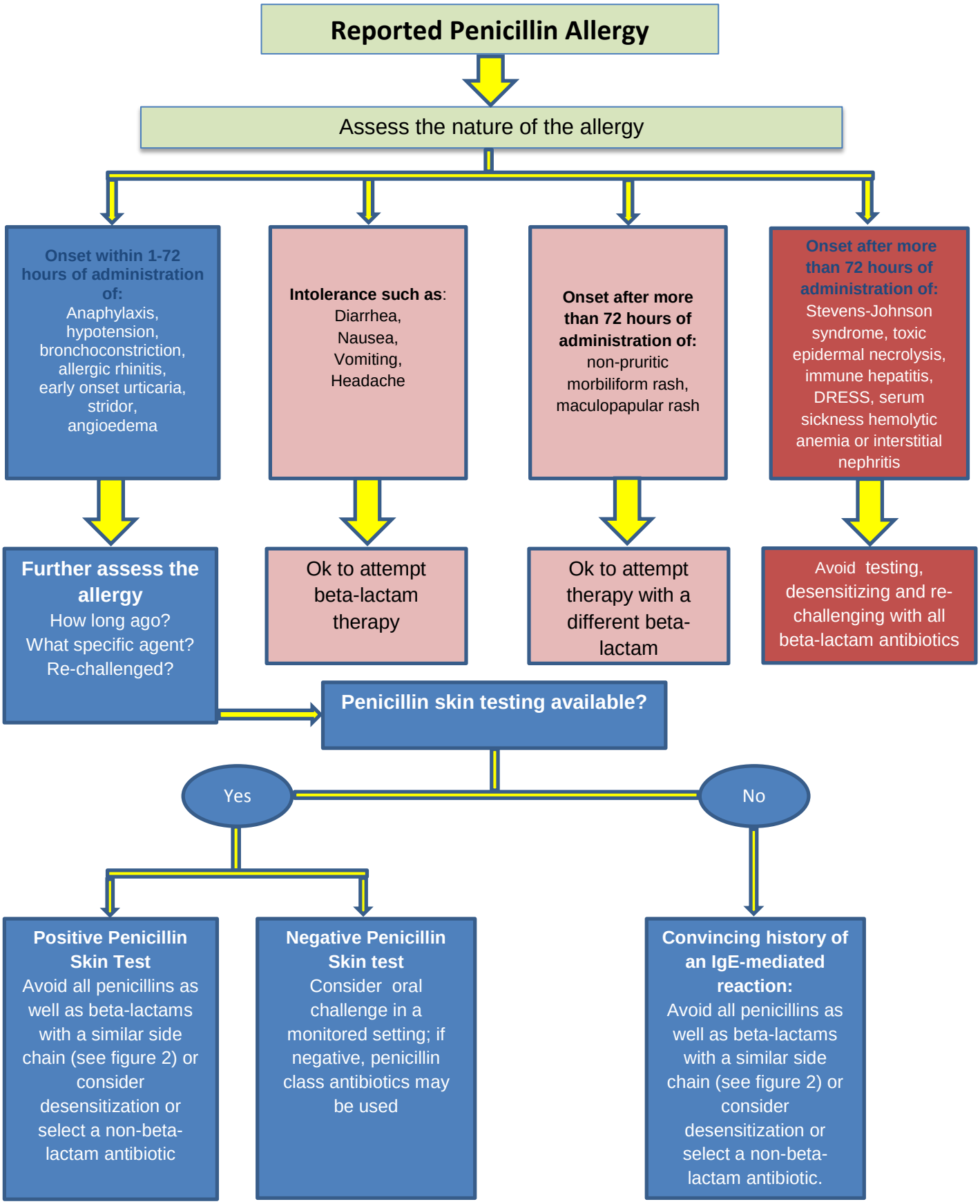
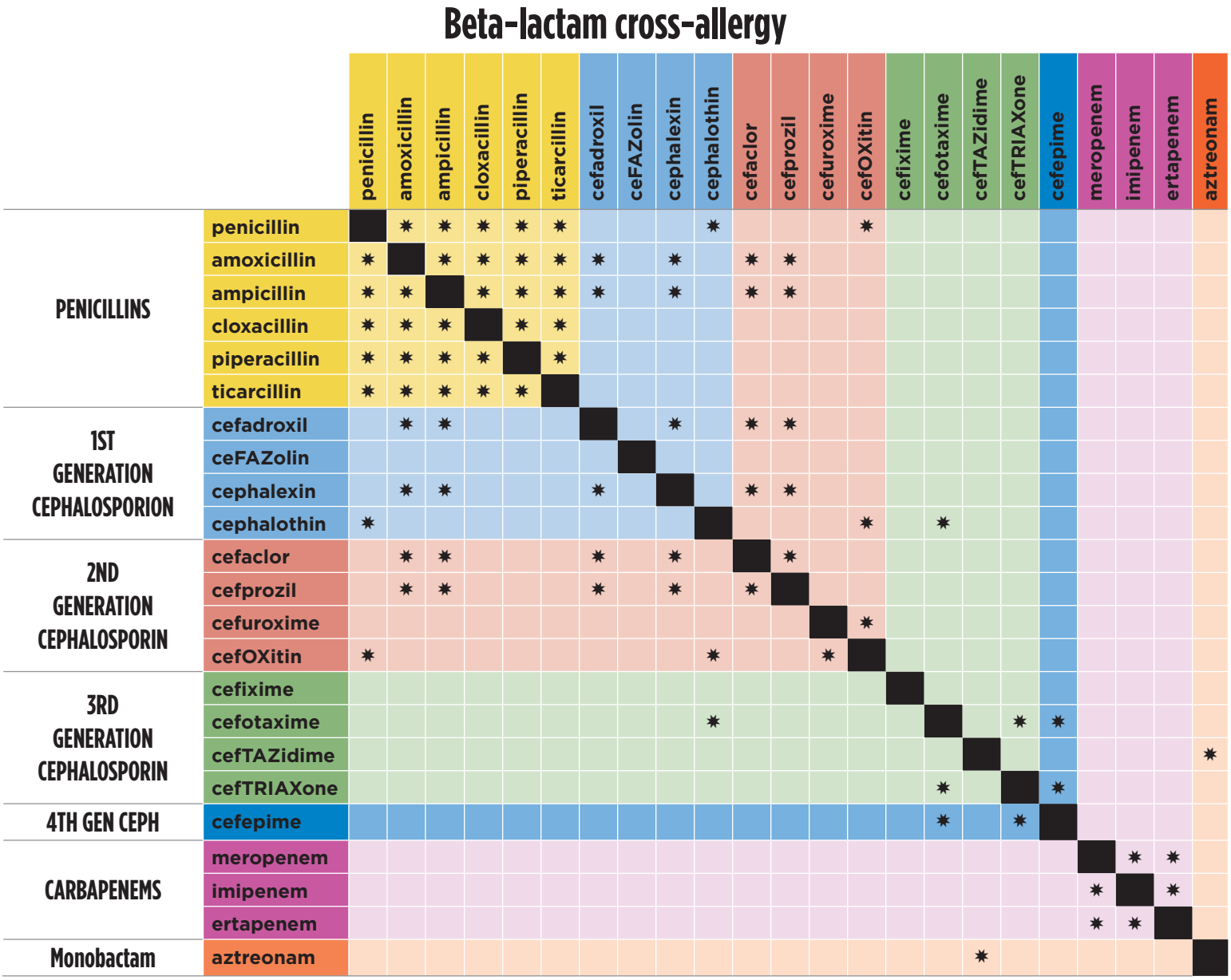


Figure 2: Matrix of Beta-Lactam Cross Allergy (based on similar core and/or side chain structures) [5, 6, 7, 8, 9]

Each '✱' in the matrix indicates side-chain and/or major/minor antigenic similarity between two antibiotics. For type-1 immediate hypersensitivity there is a risk of cross-allergenicity between pairs due to similar side-chains and/or major/minor antigenic determinants, use NOT recommended without desensitization.

For example: a patient allergic to amoxicillin would likely manifest a reaction to ampicillin, cloxacillin, piperacillin, ticarcillin, cefadroxil, cephalexin, cefaclor and cefprozil but NOT to ceFAZolin, cefuroxime or cefTRIAXone, etc.



Therapeutic Review

Beta-lactam antibiotics are the most commonly prescribed class of antimicrobials and include penicillins, cephalosporins, carbapenems and monobactams (table 1).[9] Due to similarities in their beta-lactam ring structure it has been widely accepted that penicillins, cephalosporins and carbapenems have significant cross-reactivity with other classes of beta-lactams.[5,9,10,11] Historically it has been reported that approximately 10% of patients allergic to penicillins are also allergic to cephalosporins and up to 50% cross-reactivity has been reported between penicillins and carbapenems.[4,5,9,10,11] Therefore, it has been commonly recommended that patients with a severe allergic reaction to one class of beta-lactam antibiotic should not receive any beta-lactam antibiotic.[9] This historic over-estimation of cross-sensitivity between classes of beta-lactams is inaccurate and based on flawed methodologies.[12]

Studies have shown that physicians are more likely to prescribe antimicrobials from other classes when patients have a documented penicillin or cephalosporin allergy.[13,14] Non beta-lactam alternatives may be: less effective, more toxic, broader spectrum, more expensive and more likely to lead to infection or colonization with resistant organisms.[4,13,15,16,17] The inaccurate documentation of a penicillin allergy can lead to undesirable patient outcomes. For example, one study showed that patients with a documented penicillin allergy at admission spend more time in hospital and are more likely to be exposed to antibiotics associated with *C.difficile* and vancomycin resistant *Enterococcus.*[18] In addition they had increased prevalence rates for infections secondary to *C.difficile,* vancomycin-resistant *Enterococcus* and methicillin-resistant *Staphylococcus aureus*.[18]

Practice however is changing because allergies have been better defined and the role of the chemical structure on the likelihood of cross-reactivity is now better understood. Recent data shows that the rate of allergic cross-reactivity between penicillins and other beta-lactams is much lower than previous estimates.[4,5,9,11]

Determining the nature of the patient's reaction is an important step in differentiating between an allergic reaction and an adverse drug reaction such as nausea, vomiting, diarrhea and headache.[5,9] Immunologic reactions to medications are generally classified according to the Coombs and Gell classification of hypersensitivity reactions (see table 2).[5,9] The onset and presentation of the reaction can be used to help classify the reaction and determine whether or not a beta-lactam antibiotic may be used (table 2).[5,9] Type-1, immediate hypersensitivity reactions, are immunoglobulin (Ig) E-mediated reactions and are the only true allergic reactions where the potential risk of cross-reactivity between beta-lactams should be considered.[5,9] Type-1 immediate hypersensitivity reactions usually occur within 1 hour of exposure and typically manifest as anaphylaxis, bronchospasm, angioedema, stridor, wheezing, hypotension, urticaria or a pruritic rash.[5] The incidence of these reactions is very low.[19] Nonurticarial and nonpruritic rashes are almost certainly not IgE-mediated.[5]

Penicillins

Penicillin is the most frequently reported drug allergy and is reported in 5-10% of the population.[20,21,22] Studies have shown that between 80 and 95% or more of those patients reporting a penicillin allergy do not in fact have true hypersensitivity reactions and the vast majority of these patients can tolerate beta-lactams.[1,10,21,22,23,24,25]

The use of penicillins can be associated with a nonimmediate, nonpruritic, nonurticarial rash in up to 10% of patients that is unlikely to be IgE-mediated and most often idiopathic or T-cell mediated.[5,26] While inconvenient, these reactions have not been associated with anaphylaxis and pose no risk of cross reactivity with other beta-lactams.[26] An example is the nonpruritic maculopapular rash commonly seen after the administration of ampicillin or amoxicillin to children suffering from infectious mononucleosis secondary to the Epstein-Barr virus.[27]

Only a type-1 immediate (IgE-mediated) hypersensitivity reaction to a penicillin manifesting as: anaphylaxis, bronchospasm, angioedema, hypotension, urticaria or pruritic rash warrants the avoidance of other penicillins and cephalosporins with similar side chains.[4,5,9,11] Cross-reactivity between penicillins (figure 2) may be due to shared common antigenic determinants based on similarities in their core ring structure that is common to all penicillins and/or the side chains that distinguish different penicillins from one another; therefore, cross-reactivity cannot be based on side chain similarities alone.

Currently, there is one Health Canada-approved standardized penicillin skin test. PRE-PEN contains the major antigenic determinant of penicillin and is used to rule out a type-1 immediate (IgE-mediated) penicillin allergy. Available literature suggests that the skin test using both major and minor antigenic determinants are roughly 50-60% predictive of penicillin hypersensitivity with a 97-99% negative predictive value.[4] When penicillin skin testing is not available, the approach to penicillin allergic patients is based on their reaction history and the need for treatment with a penicillin.[28] While patients with a convincing reaction history are more likely to be allergic, those with vague histories cannot be discounted as they may also be penicillin allergic.[28] The time passed since the reaction is useful because 50-80% of penicillin allergic patients lose their sensitivity after 5 and 10 years respectively.[2,29,30]

Skin testing, desensitization or re-challenge with a beta-lactam should not be performed in those patients with a history of Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS, serum sickness, immune hepatitis, hemolytic anemia or interstitial nephritis.[5]

Cephalosporins

Cephalosporin-induced skin reactions, described as urticarial, rash, exanthema and pruritus, occur in approximately 1 to 3% of patients.[31]

Early analysis of cephalosporin use in penicillin allergic patients was complicated by the uncritical evaluation of “allergic reaction”.[5,9,11] Any adverse reaction to cephalosporins was often classified as “allergic”.[5,9,11] This, accompanied with possible penicillin contamination in early cephalosporin production, resulted in overestimations of cross sensitivity.[5,9] In addition, penicillin allergic patients are more likely to have an allergy to any drug when compared to other patients.[4,5,9,10,11] Investigations have shown that individuals with a penicillin allergy are three times more likely to develop new allergies to unrelated compounds, leading to further overestimations of cross-reactivity.[5,9,10]

Cross-reactivity between penicillins and cephalosporins is due to similarities in side chains at the C-3 or C-7 position as shown in table 3 and not similarities in beta-lactam ring structure as previously speculated.[4,5,9,11] The American Academy of Pediatrics states that the likelihood of a penicillin allergic patient reacting to a cephalosporin with a different side chain is similar to that of a non-penicillin allergic patient.[5] A prospective study with skin test or challenge dose confirmed penicillin allergy

demonstrated a 0% cross-reactivity to ceFAZolin, cefuroxime and cefTRIAXone. None of these agents share a side chain with penicillin.[32] Meanwhile the risk of cross-reactivity may be up to 40% between penicillins and cephalosporins with the similar R-group side chains.[3,33]

Cross-reactivity between cephalosporins is low because of the significant heterogeneity of the side chains at the C-3 and C-7 positions.[9,34] Therefore, if a patient has a cephalosporin allergy, one can safely prescribe another cephalosporin that has dissimilar side chains at both C-3 and C-7 positions.[34]

CeFAZolin is not expected to cross react with any penicillin or cephalosporin as it does not share a side chain with any beta-lactam.[4,34]

Carbapenems

Early studies evaluating the risk of cross-reactivity between penicillin and carbapenems found rates upwards of 47%. However, these studies had poor definitions of allergy and variable methods for determining allergy status.[9] A more recent systematic review was completed to collect and combine all published data on pediatric and adult patients reported to have a clinical history of type-1 immediate hypersensitivity (IgE-mediated) to a penicillin and/or cephalosporin who were then given a carbapenem.[35] Within the study allergic reactions were classified as proven, suspected or possible IgE-mediated and non-IgE-mediated.[35] Overall, for patients with a history of proven, suspected or possible IgE-mediated reaction to a penicillin; 4.3% (36/838) had a suspected hypersensitivity reaction to a carbapenems but only 20 were compatible with an IgE-mediated reaction and only one was considered to be proven.[35] The authors concluded that carbapenems would be a reasonable option when antibiotics are required in patients with IgE-mediated reactions to penicillins.[35] They advise that clinicians proceed with caution by administering the first dose of carbapenem in a setting where anaphylaxis can be managed and to consider giving via a graduated challenge.[35] If at any stage the patient reacts then the options are to use a carbapenem desensitization protocol or switch to a non-beta-lactam antibiotic.[35]

Desensitization

Desensitization, or temporary induction of drug tolerance, is used for patients with a documented or convincing history of type-1 immediate (IgE-mediated) beta-lactam allergy and/or positive skin test and a serious infection where non-cross-reacting alternatives are not appropriate.[2,28] The goal of desensitization is to modify a patient's immune response to allow safe treatment with the allergenic drug.[28]

Desensitization will not prevent non-IgE mediated reactions and should never be attempted in patients with reactions involving major organs or severe cutaneous reactions (e.g. interstitial nephritis, SJS, TEN, DRESS, etc.).[2]

Desensitization is performed by administering incremental doses of the allergenic drug.[3] Usually the procedure is complete within hours and starts in the microgram range.[28] Dosages are usually doubled every 15 to 30 minutes until therapeutic doses are achieved.[28] When the desensitization process is complete, treatment with the select beta-lactam should be started immediately and must not be

interrupted during the treatment course.[2,28] Desensitization is usually lost within two days of cessation and must be repeated if the beta-lactam is required in the future.[2,28]

Graduated Challenge

Graduated challenges are used when there is a low likelihood of drug allergy and differ from desensitization in that they do not alter the patient's underlying immune response to the drug in question.[28] Their purpose is to allow cautious administration in patients unlikely to be allergic when there is no intention to alter the patient's immune response.[28] If the graduated challenge is tolerated the patient is then considered not to be allergic and not at increased risk for future reactions.[28] Graduated challenges should never be performed in patients with reactions involving major organs or non-IgE mediated severe cutaneous reactions (e.g. interstitial nephritis, SJS, TEN, DRESS, etc…).[28]

The starting dose of a graduated challenge is often higher than that used for desensitization and usually only involves 2 to 3 steps and completed within hours.[28] For a graduated challenge for an intravenous antibiotic, 1% of the full dose is administered, then 10 % of the full dose, then the full dose, separated by 30 minutes to 1 hour each and under careful observation.[2,3] If at any point a reaction occurs the graduated challenge is stopped.

The decision to use a graduated challenge is based on the risk of cross-reactivity and the description and remoteness of the allergic reaction in question. Treatment options requiring desensitization or graduated challenge should be avoided in severe infections (ex. febrile neutropenia, sepsis, meningitis, etc.) where delays in appropriate drug therapy are associated with poor patient outcome, in these scenarios a non-beta lactam treatment option should be considered for empiric therapy.

Table 1: Classification of Beta-Lactams

Penicillins	Cephalosporins				Carbapenems	Monobactam
	First Generation	Second Generation	Third Generation	Fourth Generation		
penicillin ampicillin amoxicillin cloxacillin piperacillin ticarcillin	cefadroxil ceFAZolin cephalexin	cefaclor cefOXitin cefprozil cefuroxime	cefTAZidime cefixime cefTRIAXone cefotaxime	cefepime	ertapenem imipenem meropenem	aztreonam

Table 2: Coombs and Gell Classification of Hypersensitivity Reactions[4,5]

Type	Mediator	Onset	Clinical Reaction	Comments
I - Immediate and Acute hypersensitivity	IgE antibodies	Less than 1hr (Rarely up to 72 hours)	Anaphylaxis, urticaria, angioedema, hypotension, bronchospasm, stridor, pruritis	Anaphylaxis: Penicillins 0.01-0.05% Cephalosporins 0.0001-0.1% Avoid the offending agent and side chain related agents (**See Figure 2**)
II – Delayed cytotoxic antibody-mediated hypersensitivity	IgG and IgM antibodies	Greater than 72 hours	Hemolytic anemia, thrombocytopenia, neutropenia	Drug specific, avoid the offending agent
III – Antibody complex-mediated hypersensitivity	IgG and IgM complexes	Greater than 72 hours	Serum sickness, glomerulonephritis, small vessel vasculitis, drug fever	Antibody-antigen complexes precipitate in tissues and potentially affect any end organ
IV – Delayed type hypersensitivity	T-Cells	Greater than 72 hours	Contact dermatitis, pustulosis	Incidence is low. Ex: Eosinophilia, bullous exanthems, severe exfoliative dermatoses (ex. SJS/TEN), interstitial nephritis, immune hepatitis and some morbilliform or maculopapular rashes
Idiopathic Reactions	Unknown	Usually greater than 72 hours	Maculopapular or morbilliform rashes	1 – 4% of patients receiving beta-lactams Not a contraindication to future use of beta-lactam antibiotics

*Anaphylaxis: defined as serious hypersensitivity reaction that is rapid in onset and may cause death, typically involving the skin, mucosal tissue or both and either respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia) or reduced blood pressure or the associated symptoms and signs of end-organ dysfunction.

Table 3: Beta-Lactam Groups with Similar Side-Chains

Similar C-7Side Chain (Cross Reactions between agents within one group is possible)			**Similar C-3 Side Chain** (Cross reactions between agents within one group is possible)						
Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7
penicillin cefOXitin	amoxicillin ampicillin cefaclor cephalexin cefadroxil cefprozil	cefepime cefotaxime cefTRIAXone	cefadroxil cephalexin		cefotaxime cephalothin		cefuroxime cefOXitin	cefixime	cefTAZidime aztreonam

Note:

- CeFAZolin does not share a side chain with any beta-lactam and is not expected to cross react with other agents
- Amoxicillin, ampicillin, penicillin, cloxacillin, piperacillin and ticarcillin share common major allergic determinants based on similarities in their core structure and/or side chains; therefore, cross-reactivity cannot be based on side chain similarities alone

References :

1. Macy E and Ngor E. Recommendations for the Management of Beta-Lactam Intolerance. Clinic Rev Allerg Immunol 2014; 47:46-55
2. Blondel-Hill and Fryters. B-Lactam Allergy. Bugs and Drugs: An antimicrobial/infectious disease reference. 2012:87-90.
3. PL Detailed-document, Allergic Cross-reactivity Among Beta-lactam Antibiotics: An Update. Pharmacist's Letter/Prescriber's Letter. October 2013
4. Terico AT and Gallagher JC. Beta-lactam allergy and cross-reactivity. J Pharm Pract. 2014 Dec;27(6):530-44.
5. Pichichero, Michael E. A review of evidence supporting the American Academy of Pediatrics recommendations for prescribing cephalosporin antibiotics in penicillin allergic patients. Pediatrics. 2005(115):1048-55.
6. DePestel DD, Benninger MS, Danziger L, LaPlante KL, May C, *et al.* Cephalosporin use in treatment of patients with penicillin allergies. J Am Pharm Assoc. 2008; 48:530-540
7. Mirakian R, Leech SC, Krishna MT, Richter AG, Huber PAJ, *et al.* Management of allergy to penicllins and other beta-lactams. Clinical & Experimental Allergy45:300-327
8. Pichichero ME and Zagursky R. Penicillin and Cephalosporin Allergy. Ann Allergy Asthma Immunol 112(2014):404-412
9. Lagacé-Wiens P. and Rubinstein E.. Adverse reactions to B-Lactam antimicrobials. Expert Opin. Drug Saf. 2012(11):381-99.
10. Herbert ME, Brewster GS, Lanctot-Herbert M. Medical Myth: Ten percent of patients who are allergic to penicillin will have serious reactions if exposed to cephalosporins. West J Med 2000;172:341
11. Pichichero ME. Use of selected cephalosporins in penicillin allergic patients. A paradigm shift. Diagnostic Microbiology and Infectious Disease. 2007(52):13-18.
12. Pichichero ME and Casey JR. Safe use of selected cephalosporins in penicillin-allergic patients: A meta-analysis. Otolaryngology-Head and Neck Surgery 2007; 136:340-347
13. Lee CL, Zembower TR, Fotis MA, Postelnick MJ; Greenberger PA, *et al.* The Incidence of Antimicrobial Allergies in Hospitalized Patients. Arch Intern Med 2000; 160:2819-2822
14. Solensky R., Earl, H.S., Gruchalla R.S. Clinical Approach to Penicillin-Allergic Patients: A Survey. Ann Allergy Asthma Immunol 2000. Mar; 84(3):329-333
15. MacLaughlin EJ, Saseen JJ and Malone DC. Cost of β-Lactam Allergies: Selection and Costs of Antibiotics for patients with a Reported β-lactam Allergy. Arch Fam Med. 2000; 9:722-726
16. Schweizer ML, Furuno JP, Harris AD, Johnson JK, Shardell MD, *et al.* Comparative effectiveness of nafcillin or cefazolin versus vancomycin in methicillin-susceptible *Staphylococcus aureus* bacteremia. BMC Infectious Diseases 2011; 11:279

17. Stryjewski ML, Szczech LA., Benjamin, Jr DK., Inrig JK., Kanafani ZA., *et al.* Use of vancomycin or first-generation cephalosporins for the treatment of hemodialysis-dependent patients with methicillin-susceptible Staphylococcus aureus bacteremia. Clin Infect Dis 2007; 44:190-196
18. Macy E. and Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: A cohort study. J Allergy Clin Immunol 2014;133:790-796
19. Romano A and Caubet JC. Antibiotic Allerigies in Children and Adults: From Clinical Symptoms to Skin Testing and Diagnosis. J Allergy Clin Immuinol Pract 2014;2:3-12)
20. Solensky R. Allergy to β-lactam Antibiotics. J Allergy Clin Immunol. 2012; 130(6):1442-1442.e5.
21. Macy E, Schatz M, Lin CK and Poon KY. The Falling Rate of Positive Penicillin Skin Tests from 1995 to 2007. The Permanente Journal 2009;13(2):12-18
22. Borch JE., Anderson KE, Bindslev-Jensen C. The Prevalence of Suspected and Challenge-Verified Penicillin Allergy in a University Hospital Population. Basic & Clinical pharmacology & Toxicology 2006; 98:357-362
23. Frumin J and Gallagher JC. Allergic Cross-Sensitivity Between Penicillin, Carbapenem and Monobactam Antibiotics: What are the Chances? The Annals of Pharmacotherapy 2009 Feb; 43:304-315
24. Jost BC., Wener HJ and Bloomberg GR. Elective Penicillin Skin Testing in a Pediatric Outpatient Setting. Ann Allergy Asthma Immunol 2006 Dec; 97(6):807-812
25. Wong BB., Keith PK., Waserman S. Clinical History as a Predictor of Penicillin Skin Test Outcome. Ann Allergy Asthma Immunol. 2006 Aug;97(2):169-174
26. Schiavino D., Nucera E., De Pasquale T., Roncoallo C., Pollastrini E., *et al.* Delayed allergy to aminopenicillins : clinical and immunological findings. Int J Immunopathol Pharmacol 2006 Oct-Dec ; 19(4) :831-840
27. Aronson MD and Awwaerter PG. Up-to-Date Infectious mononucleosis in adults and adolesants. In. Accessed online August 2015
28. Solensky R. and Khan DA. (Editors) Joint Task Force on Practice Parameters. Drug Allergy: an Updated Practice Parameter. Ann Allergy Asthma Immunol 2010; 105:259-273
29. Blanca M, Torres MJ, Garcia JJ *et al.* Natural evolution of skin test sensitivity in patients allergic to beta-lactam antibiotics. J Allergy Clin Immunol. 1999; 103:918-924.
30. Sullivan TJ, Wedner HJ, Shatz GS, *et al.* Skin testing to detect penicillin allergy. J Allergy Clin Immunol. 1981; 68:171-180
31. KelKar P.S. and Li J.T.C. Cephalosporin Allergy. N Engl J Med 2001; 345(11):804-809
32. Novalbos A, Sastre J, Cuesta J *et al.* Lack of allergic cross-reactivity to cephalosporins among patients allergic to penicillins. Clin Exp Allergy. 2001;31(3):438-443
33. Miranda A, Blanca M, Vega JM *et al.* Cross-reactivity between a penicillin and a cephalosporin with the same side chain. J Allergy Clin Immunol 1996;98(3):571-677
34. MSH+UHN Antimicrobial Stewardship Program. Antimicrobial Stewardship Clinical Summaries-Beta-lactam Allergy. http://www.antimicrobialstewardship.com/sites/default/files/asp_simple_messaging_-_beta-lactam_allergy.pdf (accessed March 5, 2015)
35. Kula B, Djordjevic G, and Robinson JL. A Systematic Review: Can one Prescribe Carbapenems to Patients with IgE-Mediated Allergy to Penicillins or Cephalosporins? CID 2014;59(8):1113-1122

Antimicrobial Allergy Evaluation Tool

(NB Provincial Health Authorities Anti-Infective Stewardship Committee, May 2016)

Reaction (as indicated in the patient's chart ☐ or described by the patient ☐)

Personal history

☐Asthma ☐Autoimmune disease ☐Atopic dermatitis ☐Latex allergy ☐Prior anaphylaxis
☐ Multiple drug intolerance syndrome ☐ Multiple drug allergy syndrome ☐Food allergy: _____
☐Other:_____

Patient questionnaire

1. When did the reaction take place? _____
2. How old was the patient at the time of the reaction? _____
3. Does the patient recall the reaction? If not, who informed them of the reaction? _____
   _____
4. Does the patient remember which medication? _____
5. What was the medication prescribed for? _____
6. What was the route of administration? _____
7. How long after starting the medication did the reaction begin? _____
   _____
8. Describe the reaction: _____
   _____
9. Did the patient seek medical care due to the reaction? _____
10. Was the medication discontinued? If so, what happened after it was discontinued? _____
    _____
11. Did the patient have any other ongoing medical problem at the time of the reaction? _____
    _____
12. What other medications was the patient taking? Why and when were they prescribed? _____
    _____
13. Has the patient taken any similar medications before or after the reaction? If so, what was the result? ____
    _____
14. Has the patient ever experienced this reaction without intake of the suspected medication? _____
    _____

Assessment

☐ Probable **non-severe delayed hypersensitivity reaction (non-IgE mediated)**
☐ Probable **non-allergic adverse reaction or intolerance**
☐ Probable **type 1 immediate hypersensitivity reaction (IgE mediated)**
☐ Probable **severe delayed hypersensitivity reaction (non-IgE mediated)**

Completed by:_____ Date/time:_____

Table 1: Patient questionnaire[1,2,4,5,6,7,12,13,14]

Question	Comments
When did the reaction take place?	Patients with type 1 immediate (IgE-mediated) hypersensitivity reactions to penicillin may lose their sensitivity over time (50% after 5 years, and 80% after 10 years)
How old was the patient at the time of the reaction?	Certain confounding factors may be more common depending on the patient's age. (Example: viral exanthems in pediatric patients)
Does the patient recall the reaction? If not, who informed them of the reaction?	Vague histories **do not** rule out serious reactions. However, it is less likely to be a serious hypersensitivity reaction if the patient or family cannot recall the specifics of the reaction.
Does the patient remember which medication?	Knowing the specific antimicrobial which caused the reaction can help in determining safe alternatives.
What was the medication prescribed for?	Sometimes patients confuse symptoms of the condition with adverse reactions of the medication. (e.g.: *Strep. pyogenes* scarlet fever rash being confused as a drug-reaction)
What was the route of administration?	Hypersensitivity reactions can be more common when medications are administered intravenously compared to orally.
How long after starting the medication did the reaction begin?	Timeframe is essential to distinguish between an IgE-mediated immediate hypersensitivity reaction or non-IgE mediated delayed reaction.
Describe the reaction.	Obtain specific information from the patient. (Ex: if a rash; determine location, morphology, etc.)
Did the patient seek medical care due to the reaction?	Can be of value to stratify how severe the reaction was.
Was the medication discontinued? If so, what happened after it was discontinued?	Discontinuing the medication will have varying results. (e.g.: depending on the type of skin reaction, symptoms may or may not improve after discontinuation)
Did the patient have any other ongoing medical problem at the time of the reaction?	Certain viral infections [e.g. Epstein-Barr virus (EBV), Herpes simplex virus (HSV), Human immunodeficiency virus (HIV), Cytomegalovirus (CMV)] are associated with non-IgE mediated cutaneous drug reactions that are often misdiagnosed as "allergic reactions".
What other medications was the patient taking? Why and when were they prescribed?	Concomitant medications could cause or contribute to the reaction.
Has the patient taken any similar medications before or after the reaction? If so, what was the result?	Tolerance of structurally similar medications is not always indicative of tolerance of the suspected medication; however, it can assist in determining safe alternatives.
Has the patient ever experienced this reaction without intake of the suspected medication?	If the same reaction has occurred without exposure to the suspected medication, it may be caused by other factors.

Therapeutic review

Allergy evaluation is an essential component of patient care. Beta-lactams, as a class, are generally safe; allergic and adverse reactions are over diagnosed and over reported. For example, up to 10% of the population will report a penicillin allergy; but up to 95% (or more) of these patients do not have a true allergy.[4,6,11]

Fearing a potential anaphylaxis secondary to beta-lactam use, many clinicians will over diagnose penicillin allergy or simply accept a diagnosis of penicillin allergy from patients without a proper history of the reaction.[2] Studies have shown that physicians are more likely to prescribe antimicrobials from other classes when patients have a documented penicillin or cephalosporin allergy.[2,9] Non beta-lactam alternatives may be: less effective, more toxic, broader spectrum, more expensive and more likely to lead to infection or colonization with resistant organisms.[6,9] Unfortunately, a penicillin allergy label is not benign. Simply being labelled as having an allergy to penicillin increases the likelihood of prolonged hospital stay and increases the risk of infections due to *Clostridium difficile*, vancomycin-resistant *Enterococcus* (VRE), and methicillin-resistant *Staphylococcus Aureus* (MRSA).[10]

Most patients have no current physical findings that can either prove or disprove their allergy label.[2] The initial probability of a true allergy is almost always determined by the allergy history.[2] The included patient questionnaire can assist clinicians in obtaining a detailed allergy history.

A detailed investigation of the patient's allergy history is necessary to differentiate between true type 1 (IgE-mediated) immediate hypersensitivity reactions (true allergic reactions) and non IgE-mediated hypersensitivity reactions or intolerances/adverse reactions. While some of the non IgE-mediated reactions are minor, other types of reactions can be severe (e.g. interstitial nephritis, immune hepatitis, hemolytic anemia, serum sickness, Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS, etc.). Table 2 below subdivides the reactions based on the Coombs and Gell classification of hypersensitivity reactions:

Table 2: Coombs and Gell Classification of Hypersensitivity Reactions [6,7]

Type	Mediator	Onset	Clinical Reaction	Comments
I - Immediate and Acute hypersensitivity	IgE antibodies	Within 1hr (Rarely up to 72 hours)	Anaphylaxis, urticaria, angioedema, hypotension, bronchospasm, stridor, pruritis	Anaphylaxis: Penicillins 0.01-0.05% Cephalosporins 0.0001-0.1%
II – Delayed cytotoxic antibody-mediated hypersensitivity	IgG and IgM antibodies	Greater than 72 hours	Hemolytic anemia, thrombocytopenia, neutropenia	Drug specific
III – Antibody complex-mediated hypersensitivity	IgG and IgM complexes	Greater than 72 hours	Serum sickness, glomerulonephritis, small vessel vasculitis, drug fever	Antibody-antigen complexes precipitate in tissues and potentially affect any end organ
IV – Delayed type hypersensitivity	T-Cells	Greater than 72 hours	Contact dermatitis, pustulosis	Incidence is low. Ex: Eosinophilia, bullous exanthems, severe exfoliative dermatoses (ex. SJS/TEN), interstitial nephritis, immune hepatitis and some morbilliform or maculopapular rashes
Idiopathic Reactions	Unknown	Usually greater than 72 hours	Maculopapular or morbilliform rashes	1 – 4% of patients receiving beta-lactams

The time to onset of the reaction can be a helpful tool in determining if the reaction was in fact a true type 1 immediate (IgE-mediated) hypersensitivity reaction. Type 1 reactions usually occur within an hour of exposure, with the possibility of occurring up to 72 hours post-exposure, and can include anaphylaxis, urticaria, angioedema, hypotension, bronchospasm, stridor and pruritis.[5,6,7]

Cutaneous reactions

Many patients may report a "rash" as an allergic reaction; however more information should be sought to assist in defining the true nature of the reaction. Cutaneous reactions can range from non-severe delayed maculopapular rashes to life-threatening toxic epidermal necrolysis; therefore it is essential to further question the patient.

Certain infections can either cause cutaneous reactions or predispose patients to reacting to antimicrobials. Patients suffering from certain bacterial infections (e.g. *Streptococcus pyogenes*, *Mycoplasma pneumoniae*) can develop cutaneous symptoms, irrespective of which antibiotic is used.[18,22] Certain viral infections [e.g. Epstein-Barr virus (EBV), Herpes simplex virus (HSV), Human immunodeficiency virus (HIV), Cytomegalovirus (CMV)] can also directly cause cutaneous symptoms.[14,18,22] Patients suffering from these viral infections may also be at a higher risk to react to certain antimicrobials.[2,4,12,13] A notable example is the delayed morbilliform rash that often develops when patients suffering from EBV are treated with an aminopenicillin, such as amoxicillin.[4,18]

Please see table 3 below for a brief description of certain cutaneous reactions.

Table 3 – Cutaneous reactions [1,2,15,16,18,19,20,21]

Type of skin reaction	Chronology	Description
Angioedema	Onset: Usually immediate (0-6 hours) Duration: Resolution within 24-72 hours	Region(s) affected: Lips, eyelids, earlobes, tongue, mouth, larynx, genitalia Morphology: Skin-coloured circumscribed edema involving the subcutaneous tissues. (can be asymmetrical/unilateral) More details: Non-pruritic; often very frightening for patients; can be painful
DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms)	Onset: 1-8 weeks after exposure Duration: Weeks-months (even after discontinuing the suspected medication)	Region(s) affected: Classic distribution: Face, upper trunk, extremities (but can progress anywhere on the surface of the skin and can sometimes have mucosal involvement) Morphology: Most commonly begins as an erythematous, pruritic, morbilliform rash More details: Pruritis and fever usually precede cutaneous eruptions. Can cause facial edema, which can be mistaken for angioedema. Systemic systems involved: - Lymphatic: lymphadenopathy is very common - Hematologic: leukocytosis, eosinophilia, lymphocytosis - Hepatic: hepatosplenomegaly, hepatitis, elevated liver transaminases, elevated alkaline phosphatase - Renal: hematuria, proteinuria, elevated BUN and creatinine - Other: pulmonary, cardiac, neurologic
Erythema multiforme	Onset: Within 3-5 days (May include prodromal symptoms of an upper respiratory infection) Duration: Approximately 2 weeks	Region(s) affected: Often appear on the extremities (hands, palms, extensor of the forearms, soles of the feet, etc.) and can spread inwards towards the trunk. May involve mucous membranes of the mouth and genitalia. Morphology: Well-demarcated, circular, erythematous papules; often "target" or "iris"-like. More details: - Can be difficult to discern from Stevens-Johnson Syndrome - Often associated with HSV or mycoplasma infections - Fever, if present, is usually mild

Type of skin reaction	Chronology	Description
Maculopapular rash / Morbilliform rash / Exanthems	Onset: Delayed (often more than 72 hours), within the first 2-4 weeks following the initial dose Duration: Usually fades within 2 weeks	Region(s) affected: Commonly begin on head, neck or upper torso, and progress downward to the extremities. Morphology: Often bilateral and symmetrical. Usually flat, barely raised, erythematous patches (one to several mm in diameter). Can also include papules. More details: - With or without pruritis - Can develop into confluent areas - Can be the result of several mechanisms (ex: viral infection, idiopathic, etc.) - Mild eosinophilia is possible, but not common - Fever rarely associated; but is mild if present
Photosensitivity / Phototoxicity	Onset: 5-20 hours after drug + UV light exposure Duration: N/A	Region(s) affected: Areas most often exposed to the sun (ex: face, back of the hands, back and sides of the neck, extensor surfaces of the forearm, etc.). Classical presentation spares shaded areas, such as under the chin, under the nose, behind the ears. Morphology: Often resembles exaggerated sunburn, sometimes with blisters. Sharp demarcation at sites where clothing or jewelry were present during light exposure. More details: Not common with beta-lactam antibiotics
Pruritis	Onset: N/A Duration: N/A	Region(s) affected: Localized or generalized itching; more often generalized when drug induced. Morphology: Does not require visible cutaneous signs of a reaction. More details: Mechanism not always clear
Stevens-Johnson syndrome	Onset: Delayed (within 8 weeks of first exposure), but with abrupt onset of symptoms. Duration: Up to 6 weeks	Region(s) affected: Less than 10% of the body surface is affected. Can affect the skin, eyes, and mucous membranes; such as the lips, mouth, and genital mucous membranes. Morphology: Often begins with dusky red, flat lesions (sometimes target-like, similar to erythema multiforme), progressing to bullae and necrotic lesions. Leads to blisters and dislodgement of the epidermis. More details: - Is accompanied by any (or all) of: high fever, malaise, myalgia, arthralgia, headache, ocular involvement, painful stomatitis - A medical emergency; in-hospital mortality = 5-12 %
Toxic epidermal necrolysis	Onset: Delayed (within 8 weeks of first exposure), but with abrupt onset of symptoms. Duration: Up to 6 weeks	Region(s) affected: Greater than 30% of the body surface is affected. Can affect the skin, eyes, and mucous membranes; such as the lips, mouth, and genital mucous membranes. Hairy regions of the skin are often spared. Morphology: See Stevens-Johnson Syndrome; eventually can resemble extensive second degree burns More details: - Is accompanied by any (or all) of: high fever, fatigue, vomiting, diarrhea, malaise, myalgia, angina, arthralgia, headache, ocular involvement, painful stomatitis - A medical emergency; in-hospital mortality more than 30%

Type of skin reaction	Chronology	Description
Urticaria	Onset: Immediate, usually within 36 hours Duration: Rarely persist for more than 24 hours	Region(s) affected: Can occur in any location. Involves the superficial portion of the dermis, and not subcutaneous tissues. Morphology: Raised, erythematous areas of edema (wheals), sometimes with central pallor. Will often blanch with pressure. More details: - Often pruritic - May or may not be accompanied by angioedema, can progress to anaphylaxis

For more information, please see the **Management of Penicillin and Beta-Lactam Allergy** guideline prepared by the NB Provincial Health Authorities Anti-Infective Stewardship Committee.

References:

1. Demoly P, et al. Drug hypersensitivity: questionnaire. Allergy 1999, 54, 999-1003
2. Salkind AR, et al. Is This Patient Allergic to Penicillin? An Evidence-Based Analysis of the Likelihood of Penicillin Allergy. JAMA, 2001; 285;19: 2498-2505
3. Management of Penicillin and Beta-Lactam Allergy. NB Provincial Health Authorities Anti-Infective Stewardship Committee. 2016
4. Lagace-Wiens P. and Rubinstein E.. Adverse reactions to B-Lactam antimicrobials. Expert Opin. Drug Saf. 2012(11):381-99.
5. Blondel-Hill and Fryters. B-Lactam Allergy. Bugs and Drugs: An antimicrobial/infectious disease reference. 2012:87-90.
6. Teirico, Terry et al. Beta-lactam allergy and cross-reactivity. Journal of Pharmacy Practice. 2014(27): 330-41.
7. Pichichero, Michael E. A review of evidence supporting the American Academy of Pediatrics recommendations for prescribing cephalosporin antibiotics in penicillin allergic patients. Pediatrics. 2005(115):1048-55.
8. Solensky R., Earl, H.S., Gruchalla R.S. Clincal Approach to Penicillin-Allergic Patients: A Survey. Ann Allergy Asthma Immunol 2000. Mar; 84(3):329-333
9. Lee, C.L., Zembower, T.R., Fotis M.A., Postelnick, M.J.; Greenberger, P.A., *et al.* The Incidene of Antimicrobial Allergies in Hospitalized Patients. Arch Intern Med 2000; 160:2819-2822
10. Macy E. and Contreras R. Health care use and serious infection prevalence associated with penicillin"allergy" in hospitalized patients: A cohort study. J Allergy Clin Immunol 2014;133:790-796
11. Solensky R. Allergy to β-lactam Antibiotics. J Allergy Clin Immunol. 2012; 130(6):1442-1442.e5
12. Stokes S and Tankersle M. HIV: Practical implications for the practicing allergist-immunologist. Ann Allergy Asthma Immunol. 2011; 107; 1-8
13. Aota N and Shiohara T. Viral connection between drug rashes and autoimmune diseases: How autoimmune responses are generated after resolution of drug rashes. Autoimmunity Reviews. 2009; 8: 488-494
14. Tohyama M and Hashimoto K. New Aspects of drug-induced hypersensitivity syndrome. Journal of dermatology. 2011; 38: 222-228
15. UpToDate: An approach to the patient with drug allergy. Last updated 04-2015. Accessed online 10/2015
16. UpToDate: Penicillin allergy: Immediate reactions. Last updated 31-05-2015. Accessed online 10/2015
17. Trubiano J, Phillips E. Antimicrobial stewardship's new weapon? A review of antibiotic allergy and pathways to "de-labeling". Curr Opin Infect Dis. 2013; Dec; 26(6)
18. Goldsmith LA,et al.. *Fitzpatrick's Dermatology in General Medicine, 8e.* 2012
19. Litt JZ. Litt's D.E.R.M. Drug Eruptions & Reactions Manual. 18th edition. 2012.
20. UpToDate: Exanthematous (morbilliform) drug reactions. Last updated: 14/05/2014. Accessed online 10/2015
21. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: Part I. Clinical perspectives. J Am Acad Dermatol 2013; 68:693.e1.
22. Hardy R. Infections Due to Mycoplasmas. Harrison's Principles of Internal Medicine, 19e. 2015

Antimicrobial Route of Administration (IV to PO)
Therapeutic Conversion

Patients on the targeted IV antimicrobials should be assessed **within 72 hours** of the start of IV therapy and regularly thereafter for the appropriateness of IV to PO conversion based on the following criteria (see below for list of targeted antimicrobials and their renal dose adjustments).

GENERAL CRITERIA

The patient:

- ☐ is tolerating food, enteral feeds and/or other oral medications AND
- ☐ is not showing evidence of malabsorption (e.g.diarrhea/vomiting) AND
- ☐ does not have continuous nasogastric suctioning, gastrectomy, malabsorption syndrome, GI obstruction or ileostomy

ANTIMICROBIAL CRITERIA

The patient:

- ☐ is clinically improving (which may include documented improved clinical signs and symptoms of infection, normalizing white blood cell count, etc…) AND
- ☐ is hemodynamically stable AND
- ☐ has been afebrile for at least 48 hours (i.e. temperature less than 38°C) AND
- ☐ is not being treated for a condition where parenteral therapy is clinically indicated, including but not limited to: endocarditis, CNS infection, osteomyelitis, *S. aureus* bacteremia, undrained or complicated abscess, cystic fibrosis, febrile neutropenia AND
- ☐ doesn't have a pathogenic isolate showing resistance to the suggested antibiotic

Table 1: Route of Administration (IV to PO)
Conversion Protocol for Targeted Antimicrobials

Drug	IV dose	PO drug/dose	Interval
azithromycin	250 or 500 mg q24h	azithromycin 250 mg	q24h
ceFAZolin[1]	1000 mg q8h	cephalexin[1,2] 500 mg	q6h
	2000 mg q8h		
cefTRIAXone (For community-acquired pneumonia or acute exacerbation of COPD)	1000 mg q24h	amoxicillin/clavulanate[1,2] 875/125 mg	q12h
	2000 mg q24h		
ciprofloxacin[1]	400 mg q12h or q24h	ciprofloxacin[1] 500 mg	Same as IV
	400 mg q8h	ciprofloxacin[1] 750 mg	q12h
clindamycin	600-900 mg q8h or q12h	clindamycin 450 mg	q6h
metroNIDAZOLE[1]	500 mg q8h or q12h	metroNIDAZOLE[1] 500 mg	Same as IV
moxifloxacin	400 mg q24h	moxifloxacin 400 mg	q24h
levofloxacin[1]	500-750 mg q24h	levofloxacin[1] (dose same as IV)	Same as IV

[1]Dose adjustment required in renal impairment
[2]Assess for true penicillin allergy

Table 2: Antimicrobial Dosing in Renal Impairment

Drug	Usual adult dose (CrCl equal to or greater than 50 mL/min)	CrCl 30 - 49 mL/min	CrCl 10 - 29 mL/min	CrCl less than 10 mL/min
amoxicillin + clavulanate	875/125 mg q12h	no adjustment	500/125 mg q12h	500/125 mg q24h
cephalexin	500 mg q6h	500 mg q8h	500 mg q12h	500 mg q24h
ceFAZolin	1000 mg q8h	no adjustment	1000 mg q12h	1000 mg q24h
	2000 mg q8h	no adjustment	2000 mg q12h	2000 mg q24h
ciprofloxacin PO	250–500 mg q12h	no adjustment	extend interval to q24h	extend interval to q24h
	750 mg q12h	500 mg q12h	500 mg q24h	500 mg q24h
ciprofloxacin IV	400 mg IV q12h	no adjustment	400 mg q24h	400 mg q24h
	400 mg IV q8h	400 mg q12h	400 mg q24h	400 mg q24h
metroNIDAZOLE	500 mg q8h or q12h	no adjustment	no adjustment	500 mg q12h
levofloxacin	750 mg q24h	**CrCl 20-49 mL/min** 750 mg q48h		**CrCl less than 20 mL/min** 500 mg q48h
	500 mg q24h	**CrCl 20-49 mL/min** 250 mg q24h		**CrCl less than 20 mL/min** 250 mg q48h

Version: 20160317

Topic: Nevirapine (VIRAMUNE) for Perinatal HIV Transmission Prophylaxis

A decision was made in October 2013 to list nevirapine (VIRAMUNE) 10 mg/mL oral suspension on the New Brunswick Hospital Formulary.

The oral suspension dosage form of nevirapine is only available in Canada via Health Canada's Special Access Programme.

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) with an established role in the prevention of vertical transmission of HIV to neonates born to mothers who received no antenatal anti-retroviral therapy or with a recent or projected HIV viral load greater than 1000 copies/mL.[1] Nevirapine is used in combination with other antiretroviral drugs for this indication.

National Institutes of Health (NIH, 2012) guidelines recommend that HIV-exposed infants of women who received no antepartum antiretroviral prophylaxis receive 3 doses of nevirapine in the first week of life (1st dose at birth, 2nd dose 48 hours after the 1st, 3rd dose 96 hours after the 2nd). Infants weighing 1.5- 2 kg at birth receive 8 mg/dose by mouth, while those weighing greater than 2 kg receive 12 mg/dose by mouth.[2]

For women who did not receive any antiretroviral therapy during pregnancy, the British Columbia (BC, 2013) guidelines recommend a single intrapartum dose of nevirapine 200 mg as soon as possible after the onset of labour or at least 2 to 3 hours prior to caesarian section. This recommendation varies from the updated NIH guidelines, which no longer includes maternal single dose nevirapine. The BC guidelines recommend the same infant dose and schedule of nevirapine as recommended by NIH.

Canadian guidelines (2003)[3] are currently being updated.

As the likelihood of its use is deemed to be low, but the time-sensitivity for acquisition is high, a small centrally-located supply of nevirapine oral suspension is being held at the Dr. Everett Chalmers Hospital pharmacy department in Fredericton for use on request by any facility in the province.

Requests to ship nevirapine to other facilities can be made by calling the DECH pharmacy department at (506) 452-5284 (inventory) or (506) 452-5280 (dispensary) or (506) 452-5700 (switchboard after hours, ask for Administrative Officer).

Discussion with an Infectious Diseases physician is strongly encouraged.

---

[1] Money D, Tullock K, Boucoiran I, Alimenti A et al. British Columbia Guidelines for the Care of HIV Positive Pregnant Women and Interventions to Reduce Perinatal Transmission. July 23, 2013; CMA Infobase.

[2] Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1- Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf.

[3] Burdge DR, Money DM, Forbes JC, Walmsley SL, Smaill FM, Boucher M, et al. on behalf of the Canadian HIV Trials Network Working Group on Vertical HIV Transmission. Canadian Consensus Guidelines for the management of pregnancy, labour and delivery and for postpartum care in HIV-positive pregnant women and their offspring [online appendix]. CMAJ 2003; 168(13): Online-1 to Online 14. Available: www.cmaj.ca/cgi/data/168/13/1671/DC1/1

Prevention of Overwhelming Postsplenectomy Infection

Introduction

The spleen is the largest lymphatic organ in the body and its primary functions are to filter damaged red blood cells and micro-organisms from the blood and to aid in the production of antibodies to enhance the immune response.[1] Asplenic patients or patients who suffer from functional asplenia have an increased risk of infection and are at risk of contracting a syndrome known as overwhelming postsplenectomy infection (OPSI).[2] Overwhelming postsplenectomy infection has been defined as "septicaemia and/or meningitis, usually fulminant but not necessarily fatal, occurring at any time after removal of the spleen".[3] The incidence of OPSI has been difficult to establish due to a wide variation in occurrence rates among different groups of patients, but lifetime risk has been estimated at 5%.[2] Risk of OPSI has been found to be dependant on age at which splenectomy occurs, time interval from splenectomy, cause for asplenia and immune status of the patient.[4] Although the incidence of OPSI is low the estimated mortality is high (38 – 69%).[2] Therefore, prevention and early identification of OPSI has been identified as key strategies to improve patient outcome.[2] Some of the current strategies being used and recommended to decrease a patient's risk of OPSI include vaccination, communication of hyposplenic state to other healthcare providers and patient education.[1,2,5] In addition, some groups recommend either short term or lifelong prophylactic antibiotics to reduce the risk of OPSI.[8] However, the use of antibiotics for the prevention of OPSI is not evidence based and is often limited by poor compliance and antibiotic resistance; therefore, its use should be assessed on a case-by-case basis.[8] The Provincial Anti-infective Stewardship Committee (ASC) has prepared resources to facilitate recommended vaccination orders, vaccine distribution, patient education and communication to the primary care physician.

Vaccinations

Asplenic patients are at risk of OPSI with any micro-organism but particularly encapsulated bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis*.[2,4] Encapsulated bacteria are more difficult for the body to clear because they resist antibody binding and their clearance is primarily completed by the spleen.[4] Therefore, it is important that attention be paid to providing optimal protection against encapsulated bacteria using appropriate immunizations.[6] The National Advisory Committee on Immunization (NACI) currently recommends the following vaccines for adult asplenic or hyposplenic patients: pneumococcal 13-valent conjugate vaccine, pneumococcal 23-valent polysaccharide vaccine, Haemophilus influenzae type b conjugate vaccine, meningococcal ACYW-135 conjugate vaccine, all routine immunizations and yearly influenza vaccine.[6,7]

Streptococcus pneumoniae is responsible for 50 – 90% of all cases of OPSI.[4] Pneumococcal polysaccharide vaccine (PNEUMOVAX 23) provides protection against 23 serotypes of *Streptococcus pneumoniae* and is the vaccine of choice for adult patients at high risk of invasive pneumococcal disease (IPD).[6] The pneumococcal polysaccharide vaccine has been found to have an efficacy of 50 to 80% against IPD among the elderly and high risk groups.[6] However, after immunization with pneumococcal 23-valent polysaccharide vaccine antibody levels begin to decline after 5 to 10 years and the duration of immunity is unknown.[6] In an effort to improve the duration of immunity the current NACI guidelines recommend for adults with asplenia or hyposplenia, one dose of pneumococcal 13-valent conjugate vaccine (PREVNAR 13) followed at

least 2 months later by one dose of pneumococcal 23-valent polysaccharide vaccine.[6] If pneumococcal 23-valent polysaccharide vaccine has been previously received then wait 1 year before giving pneumococcal 13-valent conjugate vaccine. [10] In the case where only one vaccine can be given then it should be the pneumococcal 23-valent polysaccharide vaccine. A single life time booster of pneumococcal 23-valent polysaccharide vaccine is recommended 5 years after the initial dose. [6] The Center for Disease Control and Prevention's Advisory Committee on Immunization Practices released a statement in October 2012 with similar recommendations for all adult patients 19 years of age or greater.[10]

A single dose of Haemophilus influenzae type b (HiB) conjugate vaccine is recommended in all patients who are functionally or anatomically aslpenic and greater than 5 years of age regardless of previous Hib immunization.[5,6] Current Hib vaccine should be given at least one year after any previous dose.[6] This is despite limited efficacy data and a low overall risk of *Haemophilus influenzae* sepsis in patients greater than 5 years of age.[6]

Meningococcal ACYW-135 conjugate vaccine, **MENACTRA or MENVEO**, is recommended for all groups at high risk of meningococcal infection when long-term protection is required.[6,7] Recommendations are to give 2 doses of meningococcal ACYW-135 conjugate vaccine at least 8 weeks apart for patients with anatomic or functional asplenia between the ages of 1 – 55.[6] Based on limited evidence and expert opinion current NACI guidelines recommend that 2 doses of meningococcal ACYW-135 conjugate vaccine given 8 weeks apart is appropriate for individuals greater than 55 years of age despite lacking authorization for use in this age group.[6,7] Booster doses are recommended every 3 - 5 years in individuals vaccinated at 6 years of age or younger and every 5 years for individuals vaccinated at greater than 6 years of age.[6]

In addition, all routine immunizations and yearly influenza vaccination should be given as there are no contraindications to the use of any vaccine in patients with functional or anatomical hyposplenia. [6] When an elective splenectomy is planned, the necessary vaccines are recommended to be given two weeks before removal of the spleen. [6] In the case of an emergent splenectomy, vaccines should be given two weeks post-splenectomy or prior to hospital discharge if there is a concern that the patient may not return for vaccination. [6]

Asplenic patients are at increased risk of travel related infectious diseases, including malaria and babesiosis.[9] Expert advice should be sought prior to travel to endemic areas.

Patient Education
Education has also been cited as an essential component for successful prevention of OPSI. [2] Patients should be educated regarding their increased risk of developing life threatening sepsis, what to do at the first sign of infection, to inform all healthcare professionals of their hyposplenic state and to take appropriate precautions to prevent OPSI.[2] Education may be provided through thorough discussion and provision of appropriate reading materials.[2]

Document Updated by: Tim MacLaggan, BSc(Pharm), ACPR
Document reviewed and approved by: New Brunswick Anti-infective Stewardship Committee - September 2013

References:

1. Jones P, Leder K, Woolley I, et al. Postsplenectomy Infection: Strategies For Prevention In General Practice. Australian Family Physician 2010; 39(6):383-386
2. Moffett S. Overwhelming postsplenectomy infection: Managing Patient's at risk. JAAPA 2009; 22(7):36-39
3. Waghorn DJ. Overwhelming Infection in Asplenic Patients: Current Best Practice Measures Are Not Being Followed. J Clin Pathol 2001; 54:214-218

4. Okabayashi T, Hanazaki K. Overwhelming Postsplenectomy Infection Syndrome in Adults – A Clinically Preventable Disease. World J Gastroenterol 2008;14(2):176-179
5. Spelman D, Buttery J, Daley A, Isaacs D, Jennens I, Kakakios A, Lawrence R, Roberts S, Torda A, Watson D, Woolley I, Anderson T, Street A. Guidelines for the Prevention of Sepsis in Asplenic and Hyposplenic Patients. Int Med Journal 2008;38:349-356
6. National Advisory Committee on Immunization (NACI). Canadian Immunization Guide. Evergreen Edition. Ottawa (ON): Public Health Agency of Canada; http://www.phac-aspc.gc.ca/publicat/cig-gci/ Accessed September 5, 2013
7. National Advisory Committee on Immunization (NACI). Statement on Conjugate Meningococcal Vaccine for Serogroups A, C, Y and W135. Can Commun Dis Rep 2007; 33;(ACS-3):1-24
8. Sabatino AD, Carsetti R, Corazza GR. Post-Splenectomy and Hyposplenic States. Lancet. 2011 Apr 5.[Epub ahead of print] doi:10.1016/S0140-6736(10)61493-6
9. Watson D. Pretravel Health Advice for Asplenic Individuals. J Travel Med 2003; 10:117-121
10. Use of 13-valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine for Adults with Immunocompromising conditions: Recommendations of the Advisory Committee on Immunization Practices. Morbidity and Mortality Weekly Report 61(40);816-819 October 12, 2012

****The following clinical order set is provided as a sample only and would have to be modified to an individual zone's format for local use****

Clinical Order Set
Post-Splenectomy Vaccinations – Adult

Provincial Anti-infective Stewardship Committee

Patient:_____ **Allergies:**_____

INSTRUCTIONS

1. The following orders will be carried out by a nurse **only** on the **authority of a physician/nurse practitioner.**
2. A bullet preceding an order indicates the order is standard and should always be implemented.
3. A check box preceding an order indicates the order is optional and must be checked off to be implemented.
4. Applicable boxes to the right of an order must be checked off and initialed by the person implementing the order.
5. Date and time of administration must be recorded

Contraindications

- Hypersensitivity to any vaccine component
- Anaphylactic reaction to previous dose of any of the vaccines listed below

Vaccinations (if not received pre-operatively for elective surgeries or if not received previously)

☐ *Haemophilus influenzae* type b conjugate vaccine (ACT-HIB) 0.5 mL intramuscularly in deltoid

☐ Meningococcal ACYW-135 conjugate vaccine (MENACTRA or MENVEO) 0.5 mL intramuscularly in deltoid (additional dose of meningococcal ACYW-135 conjugate vaccine required in 2 months followed by a booster every 5 years)

Pneumococcal Vaccination:

-If pneumococcal 23-valent polysaccharide vaccine (PNEUMOVAX 23) not previously received or received greater than one year ago:

☐ Pneumococcal 13-valent conjugate vaccine (PREVNAR 13) 0.5 mL intramuscularly in deltoid (Pneumococcal 23-valent polysaccharide vaccine (PNEUMOVAX 23) required 8 weeks later if not previously received. Single lifetime booster of Pneumococcal 23-valent polysaccharide (PNEUMOVAX 23) required 5 years after first dose.)

OR

-If Pneumococcal 23-valent polysaccharide vaccine (PNEUMOVAX 23) previously received but less than one year ago then wait 1 year from that date to give Pneumococcal 13-valent conjugate vaccine (PREVNAR 13). Single lifetime booster of Pneumococcal 23-valent polysaccharide (PNEUMOVAX 23) required 5 years after first dose.

☐ Seasonal Influenza Vaccine (if not already received)

Notes

-Vaccinations should be given two weeks post-operatively (if patient remains hospitalized) or on hospital discharge

-All vaccinations may be administered simultaneously. Separate syringes and separate injection sites should be used if more than one vaccine is administered on the same day.

Adapted with permission from Antimicrobial Handbook-2010 Capital Health, Nova Scotia

Revised and Approved Feb 2014

Adult Splenectomy Vaccines
Documentation for Primary Care Provider and Public Health

Please complete and forward to patient's primary care provider and local public health office on discharge.

From: _____

Phone: _____ Fax: _____

To: Dr. _____

Fax #: _____

To: Local Public Health Office

Fax #: _____

Re. Patient Name: _____

HCN: _____

D.O.B: _____

Asplenic patients are known to be at risk of infection, and are particularly susceptible to encapsulated organisms. Vaccinations are recommended to reduce the risk of infection in this patient population.

Your patient received the following vaccinations while in hospital after splenectomy. Please update your records, and note the patient's need for future vaccinations.

☐ Meningococcal ACYW-135 conjugate vaccine (MENACTRA or MENVEO)
(2 doses, 2 months apart)
Date 1st dose given: Lot#: Dose: Administration Site:
Date 2nd dose given: Lot#: Dose: Administration Site:
A booster is recommended every 5 years

☐ Haemophilus influenzae type b conjugate vaccine (ACT-HIB)
Date given: Lot#: Dose: Administration Site:

☐ Pneumococcal 13-valent conjugate vaccine (PREVNAR 13)
Date given: Lot#: Dose: Administration Site:

☐ Pneumoccocal polysaccharide vaccine (PNEUMOVAX 23) due 8 weeks after pneumococcal 13-valent conjugate vaccine (PREVNAR 13)
Date given: Lot#: Dose: Administration Site:
A single booster dose of pneumococcal polysaccharide vaccine is recommended after 5 years.

- Yearly influenza vaccine recommended.

If you have any questions regarding these vaccinations please call the numbers above, or contact the Department of Public Health for further information.

Thank you.

This message is CONFIDENTIAL. If you received this fax by mistake, please notify us immediately.

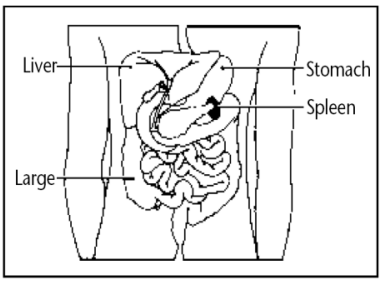
Adapted with permission from Antimicrobial Handbook-2010 Capital Health, Nova Scotia

Approved Sept 2013

Splenectomy
Information for Patients

Role of the spleen:

- The spleen has many functions, including removal of damaged blood cells. It also plays an important role in removal of certain types of bacteria.
- The spleen may be removed (*splenectomy*) if it becomes overactive, stops working or is ruptured in an accident.



Life without a spleen:

- Adults can live a normal life without a spleen. However, you may be at risk of developing infections caused by certain types of bacteria which are normally removed by the spleen.
- The most serious possible infection is called overwhelming post-splenectomy infection (OPSI). This infection is rare, but can progress rapidly and may result in the loss of limbs or death.

How to reduce the risk of infection:

- Inform all doctors, dentists and other health care professionals that you do not have a spleen.
- A series of vaccinations are recommended for patients who have their spleen removed. These vaccines are two doses of meningococcal quadrivalent conjugate vaccine, pneumococcal conjugate vaccine, pneumococcal polysaccharide vaccine (due 2 months after pneumococcal conjugate vaccine), and haemophilus influenzae type b conjugate vaccine.
- You should receive a single booster of pneumonococcal polysaccharide vaccine in **5 years**.
- You should receive a booster dose of meningococcal conjugate vaccine **every 5 years.**
- You should receive a **yearly** flu shot.
- Your family doctor will receive a letter explaining the vaccinations you received in hospital, as well as recommendations for future vaccinations.
- Seek expert medical advice before travel. Patients without a spleen are at increased risk of travel related infectious diseases, including severe malaria. Additional vaccines and/or one or more medications may be recommended to prevent or treat travel-related infectious diseases. Where malaria is endemic, preventative measures including antimalarial medications, insect repellent and barrier precautions should be used.

Identification:

- Wallet card (included with this information) includes information on vaccinations you have received.
- Medic-Alert™ bracelet should be worn. It should indicate that you had your spleen removed.

When to seek medical attention:

- If you receive a tick or animal bites/scratches. You may be at risk of developing a serious infection
- If you notice any signs of infection, including fever, sore throat, chills, unexplained cough, vomiting or diarrhea. Contact your family doctor as soon as possible for further instructions.

Adapted with permission from Antimicrobial Handbook-2010 Capital Health, Nova Scotia

Approved Sept 2013

Wallet card for Asplenic Patients

Please complete card and give to patient on hospital discharge.

Medical Alert
Asplenic Patient

Patient Name: _____
Physician Name: _____
Physician Phone: _____

Patient is at risk of potentially fatal, overwhelming infections. Medical attention required for:

- Signs of infection- fever > 38ºC, sore throat, chills, unexplained cough.
- Tick and animal bites/scratches.

Vaccination Record

Patient has received the following vaccinations:

☐ **Meningococcal ACYW-135 conjugate vaccine (MENACTRA or MENVEO)**
2 doses 8 weeks apart
Date 1st dose given: Date 2nd dose given:

☐ **Meningococcal ACYW-135 conjugate vaccine booster (MENACTRA or MENVEO)**
Dates due: every 5 years
Dates given:

☐ **Pneumococcal 13-valent conjugate vaccine (PREVNAR 13)**
Date given:

☐ **Pneumococcal polysaccharide vaccine (PNEUMOVAX 23)**
Date due: 8 weeks after pneumococcal 13-valent conjugate vaccine(PREVNAR 13)
Date given:

☐ **Pneumoccal polysaccharide booster (PNEUMOVAX 23)**
Date due: single dose 5 years after initial vaccine
Date given:

☐ **Haemophilus influenzae type b conjugate vaccine (ACT-HIB)**
Date given:

Adapted with permission from Antimicrobial Handbook-2010 Capital Health, Nova Scotia

Approved Sept 2013

Splenectomy Vaccine Checklist

1) Post-Splenectomy Vaccinations Clinical Order Set

2) Vaccines as per clinical order set plus package inserts

3) Splenectomy Vaccines – Documentation for Primary Care Provider and Public Health Form

4) Splenectomy – Information for Patients Sheet

5) Wallet Card for Asplenic Patients Sheet

References

Clostridium difficile Infection

Cohen SH., Dale NG, Stuart J, Ciaran PK, Vivian GL, McDonald LC, Pepin J &Wilcox MH. Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol 2010; 31(5):431-455

Antimicrobial Stewardship Treatment Guidelines for Common Infections. 1st Edition Vancouver Coastal Health. March 2011

McFarland LV, Elmer GW & Surawicz CM. Breaking the Cycle: Treatment Strategies for 163 Cases of Recurrent *Clostridium difficile* Disease. Am J Gastroenterol 2002;97:1769-1775

Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, McFarland LV, Mellow M & Zuckerbraun BS. Guidelines for the Diagnosis, Treatment and Prevention of *Clostridium difficile* Infections. Am J Gastroenterol 2013; 108:478-498

Debast SB, Bauer MP & Kuijper EJ. European Society of Clinical Microbiology and Infectious Diseases: Update of the Treatment Guidance Document for *Clostridium difficile* Infection. Clin Microbiol Infect 2014; 20(suppl. 2): 1 – 26

Intra-Abdominal Infections

Ball, C., Hansen, G., Harding, G., Kirkpatrick, A., Weiss, K. & Zhanel, G. (2010). Canadian practice guidelines for surgical intra-abdominal infections. Canadian Journal of Infectious Disease and Medical Microbiology, 21(1), 11-37.

Doyle, J., Nathens, A., Morris, A., Nelson, S., & McLeod, R. (2011). Best practice in general surgery guideline #4: Management of Intra-abdominal infections. Toronto, ON: University of Toronto, Faculty of Medicine.

INESSS. Antibiotic Treatment Guide: Intra-abdominal Infections in Adults. June 2012

So, M. (2010). Intra-abdominal infections education module. Toronto, ON: Mount Sinai Hospital and University Health Network.

Solomkin, J., Mazuski, J., Bradley, J, et al. (2010). Diagnosis and management of complicated intra-abdominal infections in adults and children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clinical Infectious Disease, 50 (15 January)., 133-163.

Blondel-Hill E. & Fryters S. (2012). Bugs & Drugs. An Antimicrobial/Infectious Diseases Reference. Alberta Health Services.

Young-Fadok T. & Pemberton J. (2014). Treatment of acute diverticulitis. UpToDate. Retrieved from www.uptodate.com.

Antimicrobial Stewardship Treatment Guidelines for Common Infections. 1st Edition Vancouver Coastal Health. March 2011

Antimicrobial Handbook – 2012. Editor: Dr Kathy Slayter. Antimicrobial Agents Subcommittee. Capital Health, Nova Scotia

Sawyer RG, Claridge JA, Nathens AB, Rotstein OD, Duane TM et al. Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection. N Engl J Med 2015;372(21):1996

Acute Bacterial Rhinosinusitis

Chow AW, Benninger MS, Brook I, Brozek JL, Goldstein EJ, Hicks LA, Pankey GA, Seleznick M, Volturo G, Wald ER & File TM Jr. IDSA Clinical Practice Guidelines for Acute Bacterial Rhinosinusitis in Children and Adults. Clin Infect Dis. 2012 Apr;54(8):e72-e112

Blondel-Hill E. & Fryters S. (2012). Bugs & Drugs An Antimicrobial/Infectious Diseases Reference. Alberta Health Services.

Anti-infective Review Panel. Anti-infective guidelines for community-acquired infections. Toronto: MUMS Guideline Clearhouse; 2013.

Kaplan A. Canadian guidelines for acute bacterial rhinosinusitis – Clinical summary. Can Fam Physician. 2014 Mar;60(3):227-34. Ca

Acute Exacerbation of Chronic Obstructive Pulmonary Disease

O'Donnel DE, Hernandez P, Kaplan A *et al.* Canadian Thoracic Society Recommendations for Management of Chronic Obstructive Pulmonary Disease – 2008 update – Highlights for primary care. Can Respir J 2008; 15(Suppl A):1A – 8A.

O'Donnel DE, Aaron S, Bourbeau J *et al.* Canadian Thoracic Society Recommendations for Management of Chronic Obstructive Pulmonary Disease – 2007 update. Can Respir J 2007; 14(Suppl B):5B – 32B.

Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis Management and Prevention of Chronic Obstructive Lung Disease – Update 2015. http://www.goldcopd.org/uploads/users/files/GOLD_Report_2015_Sept2.pdf Accessed September 18, 2015

Wilson R, Sethi S, Anzueto A *et al.* Antibiotics for treatment and preventions of exacerbations of chronic obstructive pulmonary disease. Journal of Infection (2013) 67, 497–515

Stockley RA, O'Brien C, Pye A *et al.* Relationship of Sputum Color to Nature and Outpatient Management

of Acute Exacerbations of COPD. Chest 2000; 117:1638–1645.

Moussaoui RE, Roede BM, Speelman P *et al*. Short-course antibiotic treatment in acute exacerbations of chronic bronchitis and COPD: a meta-analysis of double-blind studies. Thorax 2008; 63:415-422

Falagas ME, Avgeri SG, Matthaiou DK *et al.* Short- versus long-duration antimicrobial treatment for exacerbations of chronic bronchitis: a meta-analysis. J Antimicrob Chemother. 2008 May; 62: 442–450.

Siempos II, Dimopoulos G, Korbila IP *et al.* Macrolides, Quinolones and amoxicillin/clavulanate for chronic bronchitis: a meta-analysis. Eur Respir J 2007; 29:1127–1137

Wilson R, Anzueto A, Miravitlles M *et al.* Moxifloxacin versus amoxicillin/clavulanic acid in outpatient acute exacerbations of COPD: Maestral results. Eur Respir J 2012; 40:17–27

Miravitlles M, Llor C, Molina J *et al*. Antbiotic treatment of exacerbations of COPD in general practice: long-term impact on health-related quality of life. Int J COPD 2010;5:11–19

Dimopoulos G, Siempos II, Korbila IP *et al.* Comparison of First-Line with Second-Line Antibiotics for Acute Exacerbations of Chronic Bronchitis A Metaanalysis of Randomized Controle Trials. Chest 2007; 132:447–455

Leuppi JD, Schuetz P, Bingisser R *et al.* Short-term vs Conventional Glucocorticoid Therapy in Acute Exacerbations of Chronic Obstructive Pulmonary Disease The REDUCE Randomized Clinical Trial. JAMA 2013; 309(21):2223-2231

Walters JAE, Gibson PG, Wood-baker R, *et al.* Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database of Systemic Reviews 2009, Issue 1. Art. No.:CD001288. DOI"10.1002/14561858.CD001288.pub3

Anthonisen NR, Manfreda J, Warren CPW *et al.* Antibiotic Therapy in Exacerbations of Chronic Obstructive Pulmonary Disease. Ann Int Med 1987; 106:196-204

Walters JAE, Tan DJ, Whit CJ, Wood-Baker R. Different durations of corticosteroid therapy for exacerbations of chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2014, Issue 12. Art. No.: CD006897. DOI:10.1002/14651858.CD006897.pub3.

Community Acquired Pneumonia

Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Jeune IL, Macfarlane JT, Read RC, Roberts HJ, Levy ML, Wani M & Woodhead MA. British Thoracic Society Guidelines for the Management of Community Acquired Pneumonia in Adults: Update 2009. Thorax 2006; 64(Suppl III):iii1-iii55

Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF,File, TM Jr., Musher DM,Niederman MS, Torres A & Whitney CG Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults, Clinical Infectious Diseases 2007; 44:S27-72

Mandell LA, MarrienTJ, Grossman RF, Chow AW, Hyland RH and The Canadian CAP Working Group. Summary of Canadian Guidelines for the Initial Management of Community-acquired Pneumonia: An evidence-based update by the Canadian Infectious Disease Society and the Canadian Thoracic Society. Can J Infect Dis. 2000 Sep-Oct; 11(5): 237–248

Cellulitis/Erysipelas

Antibiotic Review Subcommittee of the Pharmacy & Therapeutics Committee. (2008). Update infectious disease: Community-acquired methicillin-resistant staphylococcus aureus (CA-MRSA). Skin & soft tissue infections (SSTI): Overview and Management. Vancouver Island, BC: Vancouver Health Authority.

Liu, S., Bayer, A., Cosgrove,S., Daum,S., Fridkin,S., Gorwitz,J., … Chambers, H. (2011). Clinical practice guidelines by the infectious diseases society of America for the treatment of methicillin-resistant staphylococcus aureas infections in adults and children. Clinical Infectious Diseases, 52(1 February), 1-17.

Stevens, D., Bisne, A., Chambers, H., Everett, E., Dellinger, P., Goldstein, E. … Wade, J. (2014). Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clinical Infectious Disease,41 (15, November), 1373-1406.

Mount Sinai Hospital and University Health Network Anitmicrobial Stewardship Program. (2011). Skin and skin structure infections (SSSI). Toronto, ON: Author.

Urinary Tract Infections

Blondel-Hill E. & Fryters S. (2012). Bugs & Drugs An Antimicrobial/Infectious Diseases Reference. Alberta Health Services.

Nicolle LE, Bradley S, Colgan R et al. Infectious Diseases Society of America Guidelines for the Diagnosis and Treatment of Asymptomatic Bacteriuria in Adults. Clinical Infectious Diseases 2005; 40:643-654.

Gupta K, Hooton TM, Naber KG et al. International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: a 2010 Update by the Infectious Diseases Society of America and European Society for Microbiology and Infectious Disease. Clinical Infectious Diseases. 2011; 52(5):e103-120

Hooton TM, Bradley SF, Cardenas DD et al. Diagnosis, Prevention, and Treatment of Catheter Associated Urinary Tract Infections in Adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. Clinical Infectious Diseases. 2010; 50:625-663

Hynes NA. (2013) John Hopkins Antibiotic Guide: Urinary Tract Infections in Pregnancy. Retrieved from: http://www.hopkinsguides.com/hopkins/ub/view/Johns_Hopkins_ABX_Guide/540572/all/Urinary_Tract_Infections_in_Pregnancy

Hynes NA. (2013) John Hopkins Antibiotic Guide: Pyelonephritis, Acute, Uncomplicated. Retrieved from:

http://www.hopkinsguides.com/hopkins/ub/view/Johns_Hopkins_ABX_Guide/540458/all/Pyelonephritis Acute__Uncomplicated

Hynes NA. (2013) John Hopkins Antibiotic Guide: Bacterial Cystitis, Acute, Uncomplicated. Retrieved from: http://www.hopkinsguides.com/hopkins/ub/view/Johns_Hopkins_ABX_Guide/540046/all/Bacterial_ Cystitis Acute__Uncomplicated

Hynes NA. (2013) John Hopkins Antibiotic Guide: Urinary Tract Infection, Complicated(UTI). Retrieved from:
http://www.hopkinsguides.com/hopkins/ub/view/Johns_Hopkins_ABX_Guide/540573/all/Urinary_Tract_Infection Complicated__UTI_

Coyle E.A., Prince R.A. (2011). Chapter 125. Urinary Tract Infections and Prostatitis. In R.L. Talbert, J.T. DiPiro, G.R. Matzke, L.M. Posey, B.G. Wells, G.C. Yee (Eds), Pharmacotherapy: A Pathophysiologic Approach, 8e. Retrieved February 21, 2013 from
http://www.accesspharmacy.com.libpublic3.library.isu.edu/content.aspx?aID=8004270.

Sobel JD & Kay D. (2010) Chapter 69. Urinary Tract Infections. In Gerald L Mandell. Mandell, Douglas, and Bennett's Priniciples and Practice of Infectious Disease. 7th Edition. Retrieved February 4, 2013 from http://www.expertconsultbook.com

PL Detail-Document, Choosing a UTI Antibiotic for Elderly Patients. Pharmacist's Letter/Prescriber's Letter. December 2011.

Oplinger M and Andrews CO. Nitrofurantoin Contraindication in Patients with a Creatinine Clearance Below 60 mL/min: Looking for the Evidence. Ann Pharmacother 2013; 47:106-11

Gupta K, Hooton TM, Roberts PL et al. Short-Course Nitrofurantoin for the Treatment of Acute Uncomplicated Cystitis in Women. Arch Intern Med. 2007;167(20):2207-2212

Sanchez M, Collvinent B, Miro O et al. Short-term Effectiveness of Ceftriaxone single dose in the initial treatment of acute uncomplicated pyelonephritis in women. A randomized control trial. Emerg Med J 2002;19:19-22

NOTES: