Antibiotics

Why and Why Not

2018

Academic Detailing Service

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"Seek simplicity, and mistrust it."
Alfred North Whitehead

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In preparing these materials, we reviewed treatment guidelines and randomized controlled trial evidence pertaining to each condition reviewed, local antibiogram data, Provincial stewardship resources, and national reports (CARSS 2017). Recommendations are evidence informed and incorporate local expert opinion.

All costs listed in this document are wholesale costs in Nova Scotia accessed online from McKESSON Canada in October 2018. No fees or mark-ups have been included.

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Tables, Figures and Appendices

Abbreviations

AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
AMMI	Association of Medical Microbiology & Infectious Disease
AMR	Antimicrobial resistance
ARR	Absolute risk reduction
ASB	Asymptomatic bacteriuria
CAP	Community acquired pneumonia
CI	Confidence interval
CRP	C reactive protein
DIS	Drug Information System
GAS	Group A streptococcus
IDEG	Infectious Diseases Expert Group
IDSA	Infectious Diseases Society of America
MSSA	Methicillin-sensitive *Staphylococcus aureus*
MRSA	Methicillin-resistant *Staphylococcus aureus*
NNT	Number needed to treat
RADT	Rapid antigen detection test
SIRS	Systemic inflammatory response syndrome
SSTI	Skin and soft tissue infection
TEN	Toxic epidermal necrolysis
TMP/SMX	Trimethoprim/sulfamethoxazole
UTI	Urinary tract infection
WBC	White blood cell

INTRODUCTION

Antibiotics are lifesaving when used correctly. However, these medications are a limited resource. The misuse of antibiotics has led to the global crisis of antimicrobial resistance (AMR).

Misuse of antibiotics includes:

- Unnecessary use: Prescribing an antibiotic when not indicated and of no benefit
- Underuse: Not prescribing an antibiotic when needed to treat infection
- Inappropriate use: Incorrect antibiotic choice, timing, dose, route, or duration

Unnecessary and inappropriate antibiotic use provides minimal patient benefit while still portending all the following risks of antibiotics, also known as collateral damage:

- Infection with resistant microorganisms
  - Patients getting powerful antibiotics that treat a broad range of infections are up to 3 times more likely to get another infection from an even more resistant germ. (CDC Vital signs March2014 https://www.cdc.gov/vitalsigns/pdf/2014-03-vitalsigns.pdf)
- Adverse effects in up to 20% of patients (overall, occur in ~ 1 in 10 outpatients and 1 in 5 inpatients)
  - Gastrointestinal complications (e.g. nausea and diarrhea)
    - *Clostridium difficile* infection: Most often associated with clindamycin, fluoroquinolones, β-lactams with β–lactamase inhibitors, and extended-spectrum cephalosporins.
  - Hypersensitivity reactions (e.g. rash and hives)
    - A proportion of reactions are mild and not true allergy. See β-lactam allergy (page 15) for further details. Although an allergic reaction can occur with any antibiotic, β-lactams, particularly penicillin, are the most studied.
  - Altered microbiome
  - Renal injury
  - Hematologic side effects (e.g. cytopenias)
  - Hepatobiliary effects
  - Neurological symptoms
  - QT prolongation (most often associated with macrolides and fluoroquinolones)
- Financial cost
  - In 2016, an estimated 22.6 million prescriptions were dispensed in Canadian communities, with a total expenditure of nearly 700 million dollars. At least 30% of these prescriptions were likely inappropriate.

Most antibiotics prescribed in the community are for upper respiratory tract infections, genitourinary infections, and skin and soft tissue infections.

- Antibiotics are often prescribed when not required (e.g. viral respiratory infections such as pharyngitis, acute sinusitis, acute bronchitis) or can be optimized (e.g. duration, choice, dose).

There is a need for antibiotic stewardship strategies and other preventative approaches that support the management of community-acquired infections.

- In 2016, ~ 92% of antibiotic doses dispensed in Canada were in the community.
  - Family physicians accounted for 65% of all prescriptions dispensed. (CARSS 2017)
  - The most commonly prescribed antibiotics in Canada were
    - Amoxicillin across all age groups.
    - Second was azithromycin in ages 0-59 years and ciprofloxacin in ages ≥ 60 years.
    - Ciprofloxacin was the most common antibiotic for treating UTIs among women (46%), followed by nitrofurantoin (38%) and amoxicillin (4%).
- Strategies and approaches are required to inform and assist both patients and primary care providers.

The ability to **identify and stop** inappropriate antimicrobial use is essential to slowing the emergence and spread of antimicrobial-resistant microorganisms and minimizing the associated collateral damage.

This document is an update of “Antibiotics, Why and Why Not” 2012, Dalhousie CME Academic Detailing Service. It will focus on the diagnosis and management of conditions commonly treated in the community including upper and lower respiratory tract, genitourinary, and skin and soft tissue infections.

BACKGROUND INFORMATION

Microorganisms

- Most respiratory infections are caused by viruses and DO NOT require antibiotics.
  - The most common bacterial pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae,* group A streptococcus, and M*ycoplasma pneumoniae,* depending on the site of infection.
- In the urinary tract, the most common pathogen is *Escherichia coli*.
- Skin and soft tissue infections are usually caused by β-hemolytic streptococci (groups A, B, C/G streptococci) and *Staphylococcus aureus*.

Resistance

- Resistance to antibiotics is a global health problem requiring efforts from everyone.
- Preserving the efficacy of our currently available antibiotics is essential. While there are some new antibiotics in development, novel antimicrobials will not adequately address infections due to resistant microorganisms over the long term.
- The major driver of resistance is excessive use of antimicrobials in human health and agriculture.
- Below is a range of community resistance patterns that have been collected across the province of Nova Scotia.
  - Province wide data are helpful in providing a sense of the magnitude of resistance to a given drug, but of greater value to primary care providers is to know their local community resistance data where available.
  - The following is a link to antibiograms available from the Nova Scotia Health Authority http://www.cdha.nshealth.ca/antimicrobial-stewardship-1.
- Nova Scotia community surveillance data indicate the following resistance patterns:
  - Amoxicillin:
    - *S. pneumoniae* resistance: 31%
      - However, these data are **inferred from penicillin**. Amoxicillin is not currently tested and susceptibility is higher than the reported rate in the 2017 Central Zone antibiogram. **Amoxicillin is recommended** for treating *S. pneumoniae* outpatient infections.
    - *E. coli* resistance: 30-43%
    - Group A streptococcus resistance: 0%
    - Group B streptococcus resistance: 0%

- Ciprofloxacin:
  - *E. coli* resistance: 7-23%
- Clindamycin:
  - Group A streptococcus resistance: 2-13%
  - Group B streptococcus resistance: up to 40%
  - *S. aureus* resistance: 21-23%
- Doxycycline:
  - *S. pneumoniae* resistance: 23-27%
  - *E. coli* resistance: 16-20%
- Macrolides:
  - *S. pneumoniae* resistance: 13-29%
  - Group A streptococcus resistance: 2-18%
- TMP/SMX:
  - *E. coli* resistance: 15-21%

- Resistance found in vitro does not necessarily translate into clinical failure. One theory is that antibiotics may achieve higher concentrations at the site of infection than are reflected in laboratory testing. A good example of this is the success of amoxicillin in treating pneumococcal respiratory tract infections even when the isolate is reported resistant to penicillin/amoxicillin.

Antimicrobial Stewardship

The dual purpose of antibiotic stewardship is to maximise the clinical success of antibiotics used to treat infections and to minimize the unintended consequences of their use, such as development of resistance and adverse effects.

- Prescribe antibiotics only when there is a **clear indication**.
  - Viral infections and some bacterial infections will resolve **without** antibiotics.
  - Use point of care tools/tests when appropriate
  - Avoid treating positive cultures in the absence of signs and symptoms of infection (e.g. most asymptomatic bacteriuria).

- Consider delayed prescriptions for select conditions with instructions to fill only if symptoms do not resolve or condition worsens.
  - Delayed prescriptions are particularly effective for upper respiratory infections like acute sinusitis or acute otitis media.

- Prescribe the most appropriate antibiotic
  - Limit the spectrum of activity of antibiotics to what is usually required to treat common pathogens.
    - In general, do not replace **older** antibiotics (generally more narrow spectrum and less expensive) with newer drugs unless they are substantially more effective or less toxic.
    - Reserve **fluoroquinolones** for severe infections because of their side effects, importance for other indications, and concern of developing resistance with overuse.

- Use the proper **dosage** of antimicrobial.
  - This may require high doses of some antibiotics.
  - Calculate weight-based dose in children.
  - Adjust dose in renal dysfunction as required.

- Treat for the shortest effective **duration** to minimize exposure of both pathogens and normal microbiota to antimicrobials and minimize development of resistance. Discourage saving “left-over” antibiotics for future use or giving to other people.

- If an adverse effect is experienced, provide patient education and document details to avoid labelling an adverse effect as an allergy. Many people labelled with a penicillin allergy are not truly allergic.

- Recent antimicrobial use increases the chance of resistance.
  - Highest risk within a month of therapy but can persist up to one year.
  - Increases with number & duration of antibiotic courses.

Before Starting Antibiotics

Reflect on the need and urgency of antibiotics for the specific syndrome.

Inform patients about the adverse effects of the antibiotic and when to seek care.

Take an antibiotic history. If the patient has used an antibiotic within the last 3 months, consider selecting an antibiotic from a different class.

Understand your patient's risk factors for having a resistant microorganism. The following factors are associated with increased risk of having a resistant microorganism:

- Antibiotic use in past 3 months
- Exposure to children in daycare
- Recent travel/immigration from areas with high rates of antibiotic resistance
- Exposure to healthcare facilities

Consider a second line alternative therapy if:

- The risk of resistance to first line agent is high
- There is a higher risk of complication associated with treatment failure
- A patient has not responded to first line therapy
- A patient is unable to take first line therapy due to a true allergy, intolerance, or severe drug interaction

Antibiotic Stewardship Programs and Resources

- **Local Stewardship Programs**

  The Isaak Walton Killam Health Centre and the Nova Scotia Heath Authority (NSHA) have Antimicrobial Stewardship programs that aim to improve antibiotic prescribing by promoting appropriate selection, dosing, route, and duration of antimicrobial therapy.

  - Information about the **NSHA antimicrobial stewardship team**, resources and ongoing initiatives can be found at http://www.cdha.nshealth.ca/nsha-antimicrobial-stewardship
    - Resources include:
      - Antimicrobial handbook
      - Antibiograms
      - Presentations
    - The patient populations addressed includes adults.

  - The **Isaak Walton Killam Health Centre's antimicrobial stewardship** resources are available on the **Spectrum** app http://www.spectrum.md/iwk/.
    - Resources include
      - Local Guidelines
      - Local Resistance Data
      - Local Epidemiology
      - Pathogen Information
      - Antimicrobial Information
    - The patient populations addressed include women and children.
    - As shown by the tabs provided on the link, it can be downloaded from the App Store, obtained through Google Play or viewed on the web.

- **Links to other Canadian Stewardship Initiatives**

  - Association of Medical Microbiology & Infectious Disease (AMMI) Canada. Guidance for addressing asymptomatic bacteriuria. https://www.ammi.ca/?ID=127

  - Bugs and Drugs (Alberta/BC) http://bugsanddrugs.ca/

  - Appropriateness of Care: Asymptomatic Bacteriuria. Link to evidence-based tools to assist clinicians with optimizing urine testing and identification of urinary tract infections. https://www.albertahealthservices.ca/info/Page15718.aspx

  - Sinai Health Systems-University Health Network Antimicrobial Stewardship Program
    http://www.antimicrobialstewardship.com

  - Saskatchewan Health Authority Stewardship Program
    www.rqhealth.ca/antimicrobialstewardship

  - Antibiotic Stewardship & Awareness: Links to Public Information/Patient Resources www.RxFiles.ca/ABX

  - The following link provides an example of a waiting room poster stating a commitment to not treat viral infections with antibiotics http://www.dobugsneeddrugs.org/wp-content/uploads/info-sheet-english.pdf. Posters such as this displayed in practice waiting rooms have been shown to significantly reduce antibiotic use.

  - National Collaborating Centre for Infectious Diseases (NCCID) https://nccid.ca/antibiotic-awareness/
    - Patient resources including viral prescription pads and communication materials

  - Choosing Wisely Canada https://choosingwiselycanada.org/campaign/antibiotics/

β-lactam allergy

- **Do not avoid all β-lactams** in patients reporting penicillin allergies.
  - Penicillin allergy is **over reported** and cross-allergy between penicillins and cephalosporins is **overestimated.**
    - β-lactams include all penicillins (including those combined with β-lactamase inhibitors), cephalosporins, and carbapenems. Penicillin refers to all agents in the penicillin class (i.e. penicillin V, ampicillin, amoxicillin, cloxacillin, piperacillin, etc.)

- Penicillin, amoxicillin and 1st generation cephalosporins are safe, effective, and inexpensive antibiotics.
  - Unnecessarily avoiding of their use can result in therapy that is
    - less effective
    - more toxic
    - associated with greater risk of developing antibiotic resistant microorganisms
    - more costly

- Since many people mistakenly attribute an adverse drug reaction to be an allergy, it is important to clarify whether a reaction is
  - an IgE mediated hypersensitivity reaction
  - a non-IgE mediated hypersensitivity reaction
    - non-serious (non-urticarial rash)
    - serious or life threatening
      - e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms, erythema multiforme
  - a non-hypersensitivity drug related adverse effect (e.g. GI complications, headache, yeast infections, isolated itch).

- Table 1 describes the time to onset and the presenting symptoms of the various β-lactam associated reactions, as well as recommendations on future β-lactam use.

- The incidence of a true IgE mediated hypersensitivity reaction to a β-lactam is
  - 1 to 5 per 10,000 treatment courses for penicillins
  - 0.1 to 100 per 100,000 for cephalosporins

- Individuals with IgE mediated allergies are 3 times more likely to have de novo allergies to unrelated medications.

- **Cross-reactivity** risk between **penicillin and cephalosporins** is low.
  - For IgE mediated allergies, the cross reaction between penicillin and cephalosporins is mediated by similarities for the specific chemical side chains of penicillin and cephalosporins, rather than the β-lactam ring.

- **Cross reaction among cephalosporins** is also **rare** and dependent on side-chain similarities.

Table 1: Onset, symptoms, and management options for various β-lactam associated reactions

Reaction	Onset	Symptoms	Management options
Hypersensitivity			
➢ IgE mediated	Usually <1 hour (max 72 hours)	Anaphylaxis, urticaria, angioedema, laryngeal edema, wheeze, hypotension	Do not give same drug again. Choose a cephalosporin with a different side chain. Do not give another penicillin if culprit was a penicillin.
➢ Non-IgE mediated[1]	> 72 hours	Non-serious[2] Contact dermatitis, pruritic maculopapular eruption	Not a contraindication to using a β-lactam. Consider provocation challenge.[3]
		Serious or life threatening[4] e.g. Stevens-Johnson, TEN	**AVOID all β-lactams**
Non-hypersensitivity	Anytime	Gastrointestinal symptoms, flushing during infusion, headache, yeast infection, isolated itch	Not a contraindication to using a β-lactam

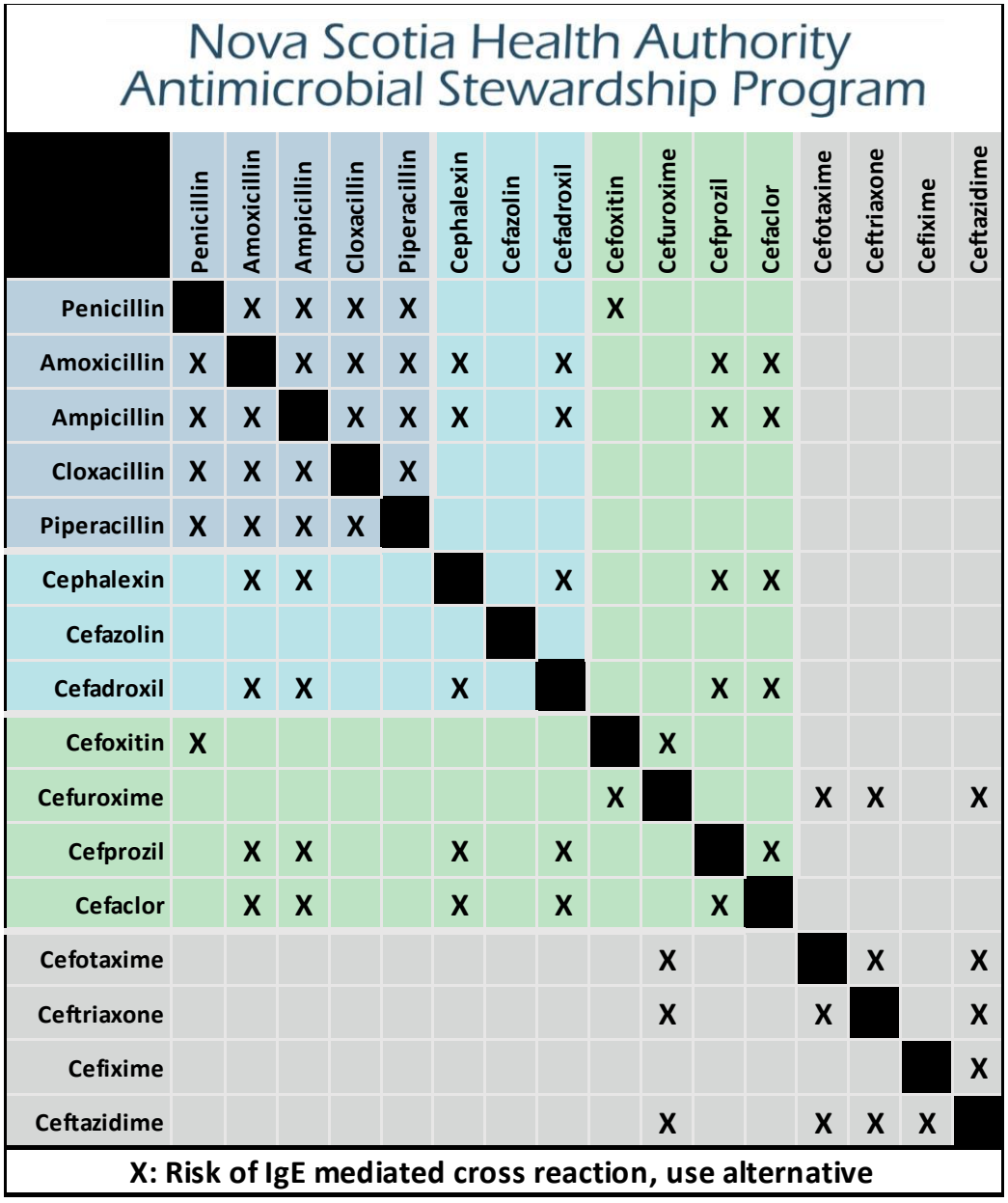
[1] Skin testing has no role in the diagnosis of non-IgE mediated reactions.
[2] > 90% of rashes occurring after people take penicillin (amoxicillin) are mild non-IgE reactions. Rashes occur in up to 7% of people.
[3] 10% of therapeutic dose, then 30 minutes later 90% of therapeutic dose. Observe for 1 hour after last dose.
[4] Serious or life threatening non-IgE mediated hypersensitivity reactions are rare with β-lactams. They include Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, erythema multiforme, or reactions that are caused by other known mechanisms (e.g., hemolytic anemia, interstitial nephritis, hepatitis).

- A complete allergic history may be helpful in the evaluation of a person reporting a penicillin allergy. Useful questions include:
  - What was the age at the time of the reaction?
  - Does the patient recall the reaction? If not, who informed them.
  - Antibiotic that caused the reaction?
  - Route of administration of agent?
  - Reaction characteristics (nature and severity)?
  - How long after starting the agent did symptoms occur?
  - What happened when agent was discontinued? When did symptoms resolve?
  - Other medications co-administered or administered near β-lactam dose?
  - Was patient hospitalized for reaction or require a doctor visit?
  - Other drugs in class tried before or after reaction? If yes, indicate drug.
    - Was it tolerated?
  - Has same reaction ever occurred without administration of offending agent?

- If unable to rule in or rule out an IgE mediated allergy, referral to an allergist is recommended.

- <u>Until assessed by an allergist</u>
  - The current understanding of IgE mediated β-lactam allergies is that it may be dependent on chemical structure of the side chains and not the β-lactam ring.
  - The following table shows β-lactams with similar side chains that may be considered to guide clinical decisions when patient has a reported allergy.
    - This consideration is based on **theoretical risk** and studies using this approach are not yet available.
  - Patients with a history suggestive of a serious or life-threatening non-IgE mediated reaction (e.g. serum sickness, Stevens-Johnson, or toxic epidermal necrosis), should **AVOID** all β-lactams.

Table 2: β-lactams with similar side chains



- Update the patient's allergy history in the medical record and Drug Information System (DIS) with any new or revised information including documentation of what was successfully administered. It is also important to inform the patient.

For adult and pediatric referrals Halifax Allergy and Asthma Associates 5657 Spring Garden Road, Suite 503 Halifax, NS, B3J 3R4 t: 902-425-3927 f: 902-425-3928	For pediatric referrals IWK Allergy Clinic t: 902-470-6554 f: 902-470-7308

Using Antibiotic Recommendation Tables in This Document

- **Green indicates 1st line treatment choices, yellow 2nd line, and red 3rd line.** Fluoroquinolones are most often listed as red choices.
- Within each colour, antibiotics are randomly listed.
- Not all antibiotics in each class are listed and others may be appropriate, for example
  - For adults, cefuroxime is listed to represent the 2nd generation cephalosporins; cefoxitin, cefprozil and cefaclor are also options.
  - For children, cefprozil is preferred over cefuroxime when possible due to better taste.
  - Clarithromycin is listed to represent the macrolide class, azithromycin is also an option.

ACUTE PHARYNGITIS

- Acute pharyngitis is typically a self-limited infection that resolves within 3 to 7 days.
- 80% to 90% of cases in adults and >70% of cases in children are viral and do not require an antibiotic.
- A minority of cases are bacterial, with group A streptococcus (GAS) the most common pathogen.
  - Although GAS pharyngitis is typically self-limited, confirmed GAS infection should receive an antibiotic to decrease the risk of complications, in particular acute rheumatic fever and pharyngeal abscesses. Antimicrobials can decrease severity of symptoms and duration by approximately 1 day.
  - Confirmation of GAS pharyngitis is achieved by throat swab culture or Rapid Antigen Detection Tests (RADT)
    - *Do not routinely do a throat swab when children present with a sore throat if they have a cough, rhinitis, or hoarseness as they almost certainly have viral pharyngitis.*
    - Up to 20% of the pediatric population may carry GAS asymptomatically.
- Most decisions to prescribe antibiotics can be guided by the total score on the following scale.

Table 3: Centor Score

Criteria	Points	Scoring[1]
Temperature >38°C	1	**≤ 1 No culture or antibiotic**
Absence of cough	1	**≥ 2 Perform culture[2] or RADT.** ✓ For negative RADT in children a back-up culture is recommended.
Swollen tender anterior cervical nodes	1	
Tonsillar swelling or exudate	1	**If either is positive for GAS, TREAT**. ✓ Treat to ↓ the risk of complications ✓ Treatment started within 9 days of confirmed GAS will prevent rheumatic fever, so wait for culture result. ✓ If antibiotics started empirically, make sure to stop if culture negative.
Age 3-14 years[3]	1	
Age 15-44 years	0	
Age ≥ 45 years	-1	

[1] This score should not be used during epidemics or in high risk populations, such as those with a history of rheumatic fever, valvular heart disease, or immunosuppression.

[2] Group C and G streptococci can cause pharyngitis but rheumatic fever has **not** been associated with these infections. GCS and GGS are not detected by RADT because they lack the group A antigen that is the target of these tests. There is no convincing evidence of benefit from antibiotics for GCS and GGS, but antibiotic therapy (same regimen as GAS) may reduce the clinical impact of the illness in severe presentations.

[3] Diagnostic testing (culture or rapid antigen detection test) is not recommended in children < 3 years unless other risk factors, such as an older sibling infected with GAS. GAS pharyngitis is uncommon in children < 3 years old.

Antibiotic	Pediatric Regimen (Acute pharyngitis)	Cost per kg per day
Penicillin V[1]	25-50 mg/kg/day divided TID or QID (maximum 3000 mg/day)	$0.03-0.09
Amoxicillin[2]	50 mg/kg/day divided once daily or BID (maximum 1000 mg/day)	$0.05
Cefprozil[3]	20 mg/kg/day divided BID (maximum 1000 mg/day)	$0.14
Cefuroxime[4]	20 mg/kg/day divided BID (maximum 1000 mg/day)	$0.15
Clarithromycin [5]	15 mg/kg/day divided BID (maximum 1000 mg/day)	$0.12
Duration of therapy is 10 days for all regimens		

Antibiotic	Adult Regimen (Acute pharyngitis)	Cost /day
Penicillin V[1]	600mg BID	$0.81
Amoxicillin	500mg BID	$0.68
Cephalexin	500mg BID	$0.90
Cefuroxime	250 mg BID	$1.44
Clarithromycin[5]	250 mg BID	$0.82
Clindamycin[5]	300 mg TID	$1.41
Duration of therapy is 10 days for all regimens		

[1] Penicillin V preferred 1st line (narrow spectrum, safe and low cost). No documented resistance to GAS.
[2] Amoxicillin broader spectrum than required, but option in children where palatable liquid preferred.
[3] 1st line option if patient **has NOT experienced a previous IgE mediated reaction** to amoxicillin.
[4] 1st line option if patient **has experienced an IgE mediated amoxicillin reaction.**
[5] Alternatives in patients unable to take β-lactams. Increased GAS resistance to clindamycin and macrolides. Also concerns with adverse effects (e.g. *C. difficile* with clindamycin).

RED FLAGS

- Improvement of symptoms should occur within 48-72 hours of the start of treatment. If there is no treatment response, an alternative diagnosis or complication should be considered.
- Individuals who experience significant difficulties swallowing, especially if associated with drooling, altered voice ("hot potato voice"), or airway obstruction (stridor) should be considered to have epiglottitis, peritonsillar abscess, or retropharyngeal abscess (suppurative complications of GAS infection) until proven otherwise.

ACUTE OTITIS MEDIA

The recommendations are not intended for treating children <6 months of age; OR for treating those with craniofacial abnormalities, immunocompromising conditions, tympanostomy tubes OR recurrent acute otitis media (AOM).

- Acute otitis media is a common, **symptomatic** infection of the middle ear.
- Most cases of symptomatic infection **do not** require antibiotic treatment as they spontaneously resolve. These cases are mild in presentation and are usually due to viruses or less virulent bacteria.
- Diagnosis
  - Symptoms usually present within one to several days and are often non-specific (e.g. fever, crying and irritability). Therefore, diagnosis depends on a **detailed examination of the middle ear** to **identify** whether or not there is probable **bacterial infection**, irrespective of the presence of fever.
    - The most common bacteria causing acute otitis media are *S. pneumoniae, H. influenza, Moraxella catarrhalis* and, less often, group A streptococci (GAS).
    - *M. catarrhalis* and some strains of *H. influenza* are less virulent, causing a mild presentation that resolves rapidly whether treated with antibiotics or not.

  - **Bacterial acute otitis media** is characterized by
    - Presence of middle ear **effusion AND**
    - Signs of middle ear **inflammation**

    - Signs of **middle ear effusion (MEE)**
      - A full or bulging tympanic membrane, OR
      - Loss of bony landmarks or presence of an air-fluid level on the tympanic membrane, OR
      - Absence or significant decreased motility of the tympanic membrane with a pneumatic otoscope

    - Signs of middle ear inflammation
      - **Bulging tympanic membrane** with
        - Distinct intense erythema or hemorrhagic patches, OR
        - Yellow in colour

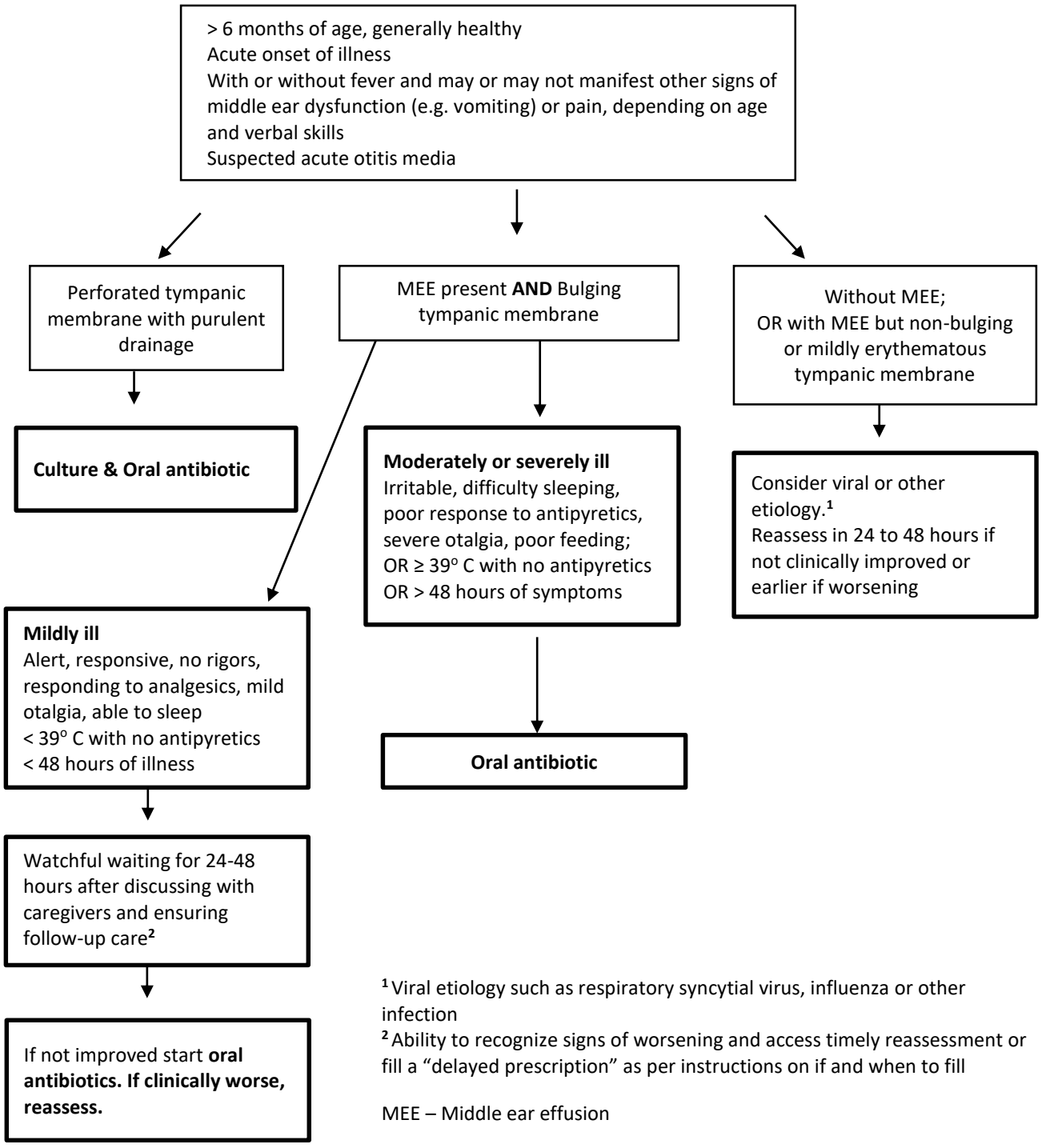
    - Visit http://otitismedia.hawkelibrary.com/aom/1_15 for images of otitis media.

- An acutely ruptured tympanic membrane in the setting of acute otitis media should always be presumed to be caused by bacteria (usually group A streptococcus) and treated with antimicrobials. A bacterial culture should be done if pus is present in the ear canal.
- Acute otitis media should be distinguished from chronic suppurative otitis media (> 3 weeks of painless ear drainage, without acute symptoms), through a previously ruptured tympanic membrane or a myringotomy tube.
- **Signs/symptoms** indicating a diagnosis **other than** acute otitis media:
  - Chronic ear drainage
  - Isolated erythema or opacity of the tympanic membrane
  - Tympanic membrane with limited mobility but no evidence of inflammation
  - Retracted or neutral position of tympanic membrane
- **RED FLAGS** indicating complicated AOM requiring emergent referral or hospital admission.
  - Suspect acute **mastoiditis** in the presence of pain and/or swelling over the mastoid bone. There can be associated petrous bone inflammation that causes unilateral facial palsy (seventh cranial nerve) and/or diplopia on lateral gaze (sixth cranial nerve palsy).
  - Venous sinus thrombosis or meningitis can manifest as a persistent or severe headache and/or cranial nerve palsies.

➢ Management

- Figure 1 below describes the management of children > 6 months of age with suspected and confirmed acute otitis media.
- In treating with an antibiotic, symptoms should improve within 24 hours and resolve within two to three days of starting the antibiotic.

Figure 1: Management of children > 6 months of age with suspected and confirmed acute otitis media
(Adapted from the Canadian Paediatric Society 2016 Position Statement Flow Diagram)



[1] Viral etiology such as respiratory syncytial virus, influenza or other infection
[2] Ability to recognize signs of worsening and access timely reassessment or fill a "delayed prescription" as per instructions on if and when to fill

MEE – Middle ear effusion

Source: Le Saux N, Robinson JL; Canadian Paediatric Society, Infectious Diseases and Immunization Committee. Management of acute otitis media in children 6 months of age and older. Paediatrics & Child Health 2016;21(1):39-44.

Antibiotic	Pediatric Regimen (Acute otitis media)	Cost/kg/day
Amoxicillin[1]	45-60 mg/kg/day Divided TID 75-90 mg/kg/day Divided BID (maximum 3000 mg/day)	$0.10 $0.19
Amox/Clav[2] 80mg/ml 7:1 formulation	Amoxicillin 45-60 mg/kg/day divided **TID**	$0.19 - $0.25
Cefprozil[3]	30 mg/kg/day Divided BID (maximum 1000 mg/day)	$0.21
Cefuroxime[4]	30 mg/kg/day Divided BID (maximum 1000 mg/day)	$0.23
Clarithromycin[5]	15 mg/kg/day Divided BID (maximum 1000 mg/day)	$0.12
Ceftriaxone	50 mg/kg/day IM or IV once daily x 3 days (reserve for emergency department)	Cost varies
Duration of therapy: **5 days for children ≥ 2 years old** **10 days for children < 2 years old; frequent recurrent AOM; perforation; or failed initially**		

[1] For known or suspected drug-resistant S. *pneumoniae* (recent {< 3 months} exposure to antibiotics, attends day care and/or unimmunized or incompletely immunized) high dose amoxicillin should be considered: 80-90 mg/kg/day divided BID or TID; Max 4 gm/day.

[2] For patients who have failed therapy with amoxicillin (symptomatic after 2-3 days of treatment).

[3] 1st line option if patient **has NOT experienced a previous IgE mediated reaction** to amoxicillin.

[4] 1st line option if patient **has experienced an IgE mediated amoxicillin reaction.**

[5] A macrolide is recommended if history is suggestive of a delayed, severe, non-IgE mediated hypersensitivity reaction to a β-lactam (*S. pneumoniae* is increasingly becoming resistant to macrolides).

ACUTE RHINO-SINUSITIS

- Almost all cases of acute sinusitis **DO NOT require antibiotics.**

For every 1000 people who enter your office with uncomplicated rhino-sinusitis
- 5 to 20 (0.5% to 2%) will have or develop bacterial rhino-sinusitis
- 4 to 17 of these patients will get better without antibiotics.

Only **1 to 3 people out of 1,000** with uncomplicated acute rhino-sinusitis **may need** an **antibiotic.**
Despite this, most patients receive antibiotics (80%)

- **Watchful waiting** is appropriate for all patients presenting with uncomplicated (no red flags) rhino-sinusitis.
  - Symptoms include facial pain, pressure or fullness, nasal obstruction and/or nasal purulence.
    - **Red flags** for urgent referral include
      - Systemic toxicity
      - Altered mental status
      - Severe headache
      - Swelling of the orbit or change in visual acuity
      - Suspected orbital or intracranial complications
  - In the first few days, viral rhino-sinusitis cannot be differentiated from early acute bacterial rhino-sinusitis.
    - Colour of nasal discharge is **not indicative** of bacterial infection.
    - Sinus X-rays are **not routinely** recommended as they too cannot differentiate between viral and bacterial.
    - Nasopharyngeal cultures are not recommended
  - Symptomatic treatments include analgesics, saline nasal drops or rinses, warm facial packs, and antihistamines (if underlying allergic rhinitis).
- The decision to prescribe an antibiotic should take into account the potential for drug related adverse events and the development of resistance, balanced with the potential for antibiotic treatment to provide a meaningful clinical benefit.
  - Potential for antibiotic benefit is more likely if
    - Symptoms > 10 days
    - Worsening after 5-7 days of initial improvement
    - Onset of severe symptoms or high fever (≥ 39°C) and purulent nasal discharge or facial pain lasting 3-4 days.

- The two main bacteria are *S. pneumoniae* and *H. influenzae.*
  - Infections due to *M. catarrhalis* are infrequent in adults but account for about 25% of cases in children.

Antibiotic	Pediatric Regimen (acute rhino-sinusitis)	Cost per kg per day
Amoxicillin	45-90 mg/kg/day Divided **TID** (maximum 3000 mg/day)	$0.10 - $0.19
Amox/Clav[1] 80mg/ml 7:1 formulation only	Amoxicillin 45-60 mg/kg/day divided TID	$0.19 - $0.25
Cefprozil[2]	15-30 mg/kg/day Divided Q12-24H (maximum 1000 mg/day)	$0.11- 0.21
Cefuroxime[3]	30 mg/kg/day Divided BID	$0.23
Clarithromycin[4]	15 mg/kg/day Divided BID (maximum 1000 mg/day)	$0.12
Duration of therapy is 10-14 days for all regimens		

[1]For fever > 39° or treatment failure with amoxicillin (symptoms not resolved after 3-5 days)
[2]1st line option if patient **has NOT experienced a previous IgE mediated reaction** to amoxicillin.
[3] 1st line option if patient **has experienced an IgE mediated amoxicillin reaction**.
[4] A macrolide is recommended if history is suggestive of a delayed, severe, non-IgE mediated hypersensitivity reaction to a β-lactam (*S. pneumoniae* is increasingly becoming resistant to macrolides).

Antibiotic	Adult Regimen (acute rhino-sinusitis)	Cost per day
Amoxicillin	500mg TID – 1000mg BID	$1.02- $1.37
Amox/Clav[1]	500 mg TID or 875 mg BID	$1.56 - $2.01
Cefuroxime[2]	500 mg BID	$2.86
Clarithromycin[3]	500 mg BID	$3.26
Doxycycline[3]	200 mg for 1st dose, then 100 mg BID	$1.17
Levofloxacin	500 mg once daily	$1.51
Moxifloxacin	400 mg once daily	$1.52
Duration of therapy is 5 to 7 days **Expect symptoms to improve but not completely disappear at the end of therapy. Some persistence of symptoms is not an indication for immediate prescription for a second antibiotic.**		

[1] For patients who have not improved or who have failed therapy with amoxicillin.
[2] 1st line option if patient has a history of penicillin allergy (IgE mediated).
[3] Options if unable to use any β-lactam (*S. pneumoniae* is increasingly becoming resistant to tetracyclines and macrolides).

ACUTE BRONCHITIS

- Acute bronchitis is viral and **DOES NOT require antibiotics**.
  - However, **most** patients **receive antibiotics (77%)** despite **no benefit** and increased **adverse effects**.
- Diagnosis
  - Acute bronchitis is inflammation of the large and mid-airways that presents with **acute cough** in absence of chronic obstructive pulmonary disease (COPD).
    - Acute cough, with or without sputum, lasts 10 days to 3 weeks (sometimes longer)
  - **Fever, tachycardia, tachypnea, hypoxia are uncommon** and suggest an alternative diagnosis (e.g. influenza or pneumonia)
  - No signs of pneumonia on physical exam. Acute bronchitis can cause wheeze.

- **RED FLAGS**: Features that warrant concern are new-onset fever, difficulty breathing, symptoms lasting >3 to 4 weeks, or bloody sputum.
  - Important to rule out alternative diagnoses.
    - Pertussis: Paroxysms of coughing, inspiratory whoop, or posttussive emesis

- Imaging is NOT routinely indicated but may be warranted in select patients.
  - Concern of pneumonia (See page 31)
  - Patients with certain comorbidities (e.g. impaired lung function, a history of smoking, immunocompromise, or chronic heart disease) who develop cough may require further investigation (e.g. chest X-ray, spirometry).

- Management
  - **No evidence of pneumonia, no role for antibiotics**

Endpoint	RR (95% CI)
Clinical improvement at follow-up	1.07 (0.99 to 1.15) no significant difference between antibiotics and placebo
Adverse effects in the antibiotic group	1.20 (1.05 to 1.36); NNH=5, primarily GI related

  - Provide reassurance, smoking cessation, supportive measures (humidifier, honey, cough suppressants), vaccination.
  - Consider other causes of cough > 3 weeks with normal X-ray: GERD, postnasal drip, asthma, ACE inhibitor use.

ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (AECOPD)

- The chronic and progressive course of COPD is interspersed with **acute exacerbations**.
  - AECOPD is defined as an acute, sustained worsening of dyspnea, cough, and/or sputum production.
  - Sustained implies a change from baseline lasting 48 hours or more.

- Causes of acute exacerbations
  - Viral in 30-50% of exacerbations
    - Rhinovirus most common
  - Bacteria
    - *H. influenzae*
    - *S. pneumoniae*
  - Non-infectious
    - Irritants, allergens, pollution
    - Pulmonary embolism
    - Cardiac decompensation

- Management
  - **Outpatient management** is recommended for mild to moderate exacerbations (no red flags)
  - Pharmacologic therapies include
    - An increase in dose &/or frequency of inhaled **short-acting bronchodilators** (β_2 agonist +/- anticholinergics ideally delivered by MDI with valve holding chamber)
      - Adequate to improve symptoms in mild exacerbations
    - Corticosteroid (Prednisone 50mg or equivalent orally daily for 7 days)
    - Antibiotic **in some situations**
      - Recommended if **increased purulence** (change in sputum color) + increased dyspnea/increased sputum volume
        - Antibiotic recommendations differ if AECOPD is precipitated by pneumonia (confirmed by new changes on chest x-ray). See CAP page 31 for antibiotics.
      - CRP and WBC not helpful in determining antibiotic need as they can be elevated in both bacterial and viral causes.

- **Red flags for hospitalization** include
  - Severe symptoms (e.g. sudden worsening of resting dyspnea, high respiratory rate, hypoxia, confusion, drowsiness)
  - Acute respiratory failure
  - Onset of new physical signs (e.g. cyanosis, peripheral edema)
  - Failure of an exacerbation to respond to outpatient/initial medical management
  - Presence of serious comorbidities (e.g. heart failure, newly occurring arrhythmias)

Antibiotic	Regimen for AECOPD	Cost per day
Simple (low risk patient)		
Doxycycline	200 mg for 1st dose then 100 mg BID	$1.17
Amoxicillin	500 mg TID – 1000mg BID	$1.02 - $1.37
Cefuroxime	500 mg BID	$2.86
Clarithromycin[1]	500 mg BID	$3.26
Complicated (high risk) patients[2] or treatment failure[3]		
Amox/Clav	500 mg TID or 875 mg BID	$1.56 - $2.01
Levofloxacin	500 mg once daily	$1.51
Moxifloxacin	400 mg once daily	$1.52
Risk for *P. aeruginosa* (Previous isolation of *Pseudomonas*, advanced COPD, concomitant bronchiectasis, frequent/recent antimicrobial use)		
Ciprofloxacin[4]	500 mg BID	$1.00
Duration of therapy is usually 5 to 7 days. **Expect symptoms to improve but not completely disappear at the end of therapy.** **Symptoms may not completely resolve for several weeks.**		

[1]Clarithromycin should be reserved for when allergy restricts use of other agents as it is less effective against *H. influenzae* and *S. pneumoniae*.

[2] **Complicated** patients have any **one** of the following risk factors:
- FEV_1 < 50% predicted
- ≥ 4 exacerbations per year
- Significant cardiac disease (e.g. ischemic heart disease, heart failure)
- Use of home oxygen
- Use of chronic oral steroids

[3]Clinical deterioration after 72 hours or no improvement with first line treatment.

[4] Poor coverage of *S. pneumoniae* and should not be routinely used in AECOPD.

- Review strategies to decrease the risk of recurrence such as
  - optimal use of maintenance medications and puffer technique
  - smoking cessation
  - vaccinations
  - pulmonary rehabilitation
  - INSPIRED program (http://chdintra.cdha.nshealth.ca/forms/inspiredCOPDReferralForm.pdf)

ADULT COMMUNITY ACQUIRED PNEUMONIA (CAP)

- Many microorganisms cause CAP, including viruses and bacteria.
- The usual causative bacterial microorganism is *S. pneumoniae.*
  - *H. influenzae* is a relatively uncommon cause of CAP, and β-lactamase production occurs in < 25% of cases.
  - Atypical microorganisms are the cause of a small portion of CAP cases.
- Diagnosis
  - Diagnosis is based on clinical presentation AND infiltrate on chest x-ray.
    - Clinical symptoms suggestive of CAP include fever, cough, sputum production, pleuritic chest pain, dyspnea, tachypnea, and tachycardia.
    - Physical findings consistent with consolidation (e.g. dullness to percussion, increased tactile fremitus, reduced normal vesicular breath sounds and increased bronchial breath sounds)
  - Consider alternative diagnoses such as influenza, acute bronchitis, congestive heart failure, pulmonary embolism, and AECOPD.
  - Patients who show an initial lack of infiltrate on x-ray should be advised to seek re-evaluation if a high clinical suspicion of pneumonia remains or increases within 48 to 72 hours, at which time the chest x-ray should be repeated.
  - Need for hospitalization can be guided by clinical judgement or the **CRB-65** score.

CRB-65		
Criteria		**Points**
Confusion: <u>b</u>ased upon a specific mental test or new disorientation to person, place, or time		1
Respiratory rate ≥ 30 breaths/minute		1
Low **b**lood pressure (systolic < 90 mm Hg; or diastolic < 60 mmHg)		1
Age ≥ **65 years**		1
Score[1]	**30 day mortality**	**Management setting**
0 (plus O_2 sat >92% on room air)	2.4%	Can be treated as outpatients
1 - 2	13.3%	Consider admission to hospital ward
3 - 4	34.3%	Often require ICU care

[1] Ratings may change over a short period of time and repeat assessments over several hours may be necessary.

- Management of patients NOT requiring Intensive Care Unit admittance (outpatient or admitted to ward)
  - **Routine coverage** of atypical bacteria with a macrolide **has not been proven** to be of benefit in outpatients or those admitted to non-ICU hospital wards.
  - In the 2017 Central Zone antibiogram, resistance of *S. pneumoniae* to amoxicillin is quite high. However, this is inferred from penicillin. Amoxicillin is not currently tested and susceptibility is higher than reported in the antibiogram. Use is recommended as quoted susceptibility does not reflect successful oral treatment with amoxicillin.
  - Modifications to and/or expert advice on the recommendations below should be considered in patients at risk for antimicrobial resistant microorganisms (e.g. recent antimicrobial therapy or structural lung disease)
  - Referral/expert advice is recommended for patients with significant immunocompromise. Alteration of empiric therapy choice may be required.
    This includes patients with:
    - Recent or current use of immunomodulating drugs
    - HIV with low (known or suspected) CD4 count
    - Solid organ transplantation
    - Stem cell transplantation
    - Chemotherapy-associated neutropenia

CRB-65 score 0 plus O2 sat > 92% on room air Can be treated as outpatients		
Antibiotic	**Adult CAP regimen**	**Cost per day**
Amoxicillin	1000 mg BID	$1.37
Doxycycline[1,2]	200 mg for 1st dose then 100 mg BID	$1.17
Cefuroxime[2]	500mg BID	$2.86
Levofloxacin[3]	750 mg once daily	$3.96 - $6.55
Moxifloxacin[3]	400 mg once daily	$1.52
Duration of therapy is usually 5-7 days		

[1] 1st line option if history is suggestive of a delayed, severe, non-IgE mediated hypersensitivity reaction to a β-lactam

[2] 1st line option if patient has a history of penicillin allergy (IgE mediated)

[3] 2nd line options in patients failing amoxicillin (worsening after 72 hours or no response after completion of therapy) and if there is no fluoroquinolone use in previous 3 months

CRB-65 score 1-2 Consider admission to hospital ward		
Antibiotic	**Adult CAP regimen**	**Cost per day**
Amoxicillin	1000 mg BID	$1.37
Amox/Clav	875 mg BID	$1.56
Cefotaxime[1]	1000 mg Q8H IV	$24.99
Ceftriaxone[1]	1000 mg Q24H IV	$12.49
Levofloxacin[2]	750 mg once daily	$3.96 - $6.55
Moxifloxacin[2]	400 mg once daily	$1.52
Duration of therapy is usually 5-7 days		

[1] 1st line option if patient has a history of penicillin allergy (IgE mediated)

[2] 1st line option if β-lactam contraindicated

PEDIATRIC COMMUNITY ACQUIRED PNEUMONIA (CAP)

- Viruses are the most frequent cause of pneumonia in the first 5 years of a child's life. Viruses as a sole cause of pneumonia are less common in older children, with the exception of influenza.

- When bacterial
  - *S. pneumoniae* is the most common pathogen.
  - Group A streptococcus is less common.
  - *H. influenza* type b is very rare due to vaccination.
  - *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are more common causes in children > 5 years but occasionally cause pneumonia in younger children.

- Diagnosis of bacterial pneumonia
  - Symptoms may be nonspecific, especially in infants and younger children.
  - Common symptoms include acute onset of fever, cough, difficulty breathing, lethargy, and poor feeding or vomiting.
    - Chest or abdominal pain may also be prominent features.
    - Abrupt onset of rigors favours a bacterial cause.
    - *M. pneumoniae* is typically characterized by malaise and headache for 7 to 10 days before the onset of fever and cough, which then predominate.
  - Children typically experience fever and tachypnea (determined by counting the respiratory rate for 60 s in a calm state).

Table 5: Age-specific criteria for tachypnea

Age	Approximate normal respiratory rate	Upper limit for defining tachypnea
< 2 months	34 – 50	60
2 – 12 months	25 – 40	50
1 – 5 years	20 – 30	40
>5 years	15 – 25	30

Source: Canadian Paediatric Society, Uncomplicated pneumonia in healthy Canadian children and youth: Practice points for management 2015
https://www.cps.ca/en/documents/position/pneumonia-management-children-youth

  - Physical signs of consolidation include dullness to percussion, increased tactile fremitus, reduced normal vesicular breath sounds, and increased bronchial breath sounds – all of which may be difficult to detect in young children.

- Optimally, the diagnosis of bacterial pneumonia should be supported by a chest X-ray before starting antimicrobials.
  - It is difficult to differentiate bacterial pneumonia from other conditions such as viral infections or reactive airway disease based on clinical presentation alone.
  - In bacterial pneumonia, there is likely to be a much more visible presence of infiltrate in the lungs than viral pneumonia.

➢ Management

- Most children with pneumonia can be managed as outpatients.
- Hospitalization is generally indicated if a child
  - has inadequate oral intake
  - is intolerant of oral therapy
  - has severe illness or respiratory compromise requiring O_2

Antibiotic	Regimen for Outpatient Pediatric CAP (Age > 3 mon)	Cost per kg per day
Amoxicillin	45-90[1] mg/kg/day Divided **TID** (maximum 4000 mg/day)	$0.09 - 0.19
Cefprozil[2]	15-30 mg/kg/day Divided once daily to BID (maximum 1000mg/day)	$0.11- 0.21
Clarithromycin[3]	15 mg/kg/day Divided BID (maximum 1000 mg/day)	$0.12
Duration of therapy is 7 to 10 days for all regimens		

[1] Use higher dose (75-90 mg/kg/day) if patient has any of the following risk factors for resistant *S. pneumoniae*
- Unimmunized or incompletely immunized
- Daycare attendance
- Use of antibiotics in the preceding 3 months
- Failure of initial treatment

[2] 1st line option if patient **has NOT experienced a previous IgE mediated reaction** to amoxicillin. Neither cefprozil nor clarithromycin cover *S pneumoniae* as well as amoxicillin and cefprozil does not cover *C. pneumoniae* and *M. pneumonia.*

[3] 1st line option for patients with IgE mediated penicillin allergy. A macrolide is also recommended if history is suggestive of a delayed, severe, non-IgE mediated hypersensitivity reaction to a β-lactam (*S. pneumoniae* is increasingly becoming resistant to macrolides but they do cover *C. pneumoniae* and *M. pneumoniae.*)

URINARY TRACT INFECTIONS

- The spectrum of urinary tract infections (UTI) includes:
  - Acute uncomplicated cystitis (bladder infection)
  - Recurrent cystitis (repeated bladder infection)
  - Prostatitis (prostate infection)
  - Pyelonephritis (kidney infection)
  - Catheter-associated UTI (in individuals with indwelling urinary catheters)

- Complicated UTI
  - A standard definition of complicated UTI is lacking but broadly includes
    - infection outside of the bladder (i.e. kidneys or prostate) OR
    - the presence of ≥1 of the following risk factors
      - Pregnancy
      - Immunosuppression
      - Diabetes (especially if long term complications)
      - Indwelling catheter
      - Anatomical abnormality
      - Voiding dysfunction
      - Obstruction
      - Recent urogenital procedure

- The spectrum of UTIs are sometimes broadly classified as upper and lower UTIs.
  - Lower UTI involves the urethra, bladder, and prostate gland.
  - Upper UTI refers to kidney infection.

- The remainder of this section will focus on uncomplicated cystitis.

Acute Uncomplicated Cystitis

- Cystitis is an **infection** of the bladder, usually caused by bacteria from the gastrointestinal tract entering the urethra and travelling up to the bladder.
- The most common **infecting bacteria** is *E. coli.* Other less common bacteria include *Proteus* and *Klebsiella* species.
- Diagnosis
  - A **diagnosis** of acute uncomplicated cystitis is **dependent on** the presence of **symptoms** such as dysuria, urgency, frequency, suprapubic pain or tenderness.
    - If dysuria, urgency, and frequency are present, there is an approximate 90% chance of an accurate clinical diagnosis.
    - The same bacteria can be present in the bladder and not cause symptoms. In this case they are colonizing bacteria as opposed to infecting bacteria. This is referred to as asymptomatic bacteriuria. **Antibiotics** are **not recommended** for most cases of **asymptomatic bacteriuria** as it is **not** an **infection.**
  - The reliability of the urine dipstick as a diagnostic tool is low due to an inability to differentiate between an infection and asymptomatic bacteriuria, and is not recommended as a test for diagnosing UTI.
  - In infants and children,
    - Please refer to the Canadian Paediatric Society position statement available at https://www.cps.ca/en/documents/position/urinary-tract-infections-in-children for complete details.
    - If symptoms suggest a UTI (dysuria, urinary frequency, hematuria, abdominal pain, back pain or new daytime incontinence), it should be ruled out.
      - In toilet-trained children, a midstream urine sample should be collected for urinalysis and culture.
      - UTI is unlikely if the urinalysis is completely normal.
      - A bagged urine sample may be used for urinalysis but should not be used for urine culture.
  - It is important to rule out complicated infections, including those extending beyond the bladder (i.e. pyelonephritis) as they require different management.
    - Cystitis in men is often, but not always, considered complicated. Investigation for anatomical abnormalities or prostatitis should be considered.
- **Red Flags** - Symptoms and signs suggesting a diagnosis other than acute uncomplicated cystitis include
  - Fever, chills, nausea, or vomiting
  - Back pain, flank pain and tenderness
  - Perineal, penile or rectal pain, penile discharge, tender prostate on rectal examination
  - Vaginal discharge

- **Urine culture** is **not** generally recommended unless
  - Antibiotic use or UTI in last 3-6 months
  - Suspected UTI in a man
  - Travel outside North America in last 6 months
  - Recent hospitalization
  - History of a UTI caused by a multidrug resistant microorganism
  - Complicated UTI
  - Failure to respond to empiric therapy after 48 hours
    - **Post treatment** urine cultures are usually **not recommended if adequate response** to therapy. However, they are sometimes obtained in patients with recurrent relapsing UTIs.

- Management
  - Provide advice about managing symptoms with self-care
    - Consider acetaminophen or ibuprofen for pain
    - Maintain adequate intake of fluid
    - No evidence of benefit for cranberry products to treat a lower UTI.
  - Empiric outpatient treatment

Antibiotic	Pediatric (> 2 months) EMPIRIC Therapy Acute uncomplicated cystitis	Cost per kg per day
Cephalexin	50mg/kg/day divided QID (maximum 4000 mg/day)	$0.64
Cefixime[1]	8 mg/kg/day once daily (maximum 400mg/day)	$0.19
Amoxicillin[2]	50mg/kg/day divided TID (maximum 3000 mg/day)	$0.05
TMP/SMX[1]	8mg/kg/day divided BID Dose based on TMP component (maximum 160 mg TMP per single dose)	$0.20
Recommended duration of therapy 5 to 7 days		

[1] Option if history of penicillin allergy (IgE mediated)
[2] Only use empirically if *Enterococcus* suspected as there are high rates of resistance with *E. coli* and poor activity vs *Klebsiella*

Antibiotic[1]	Adult Regimen for EMPIRIC Therapy Acute uncomplicated cystitis	Cost per course
Nitrofurantoin Monohydrate/ macrocrystals[2]	100mg BID Women 5 days: Men 7 days	$7.86 - $11.00
TMP/SMX[3]	1 DS tab BID Women 3 days: Men 7 days	$0.72 - $1.68
Cephalexin	500mg QID Women 5-7 days: Men 7 days	$9 - $12.60
Amoxicillin-clavulanate	875 mg BID Women 5-7 days: Men 7 days	$7.75 – $10.85
Fosfomycin[4]	3 g X 1 dose (Women) 3 g every 72 hrs X 3 doses (Men)	$15.23 $45.69
Ciprofloxacin	250 mg BID Women 3 days: Men 7 days	$2.67 - $6.23

[1] Other antibiotics are appropriate if culture confirms susceptibility. Moxifloxacin should not be used because it does not attain sufficient concentration in the urine.

[2] Nitrofurantoin should not be used in patients with

- CrCl < 30 ml/min
- Pyelonephritis or prostatitis due to poor distribution into serum and tissue

[3]TMP/SMX

- Regular monitoring of kidney function and electrolytes are recommended for patients at risk of hyperkalemia, such as those with
  - baseline renal **dysfunction**
  - an age > 65 years
  - prolonged duration of TMP/SMX therapy
  - concomitant therapy with angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or potassium sparing diuretics (e.g. spironolactone)

[4] Fosfomycin should not be used in patients with pyelonephritis due to poor distribution into serum and tissue.

Antibiotic	Regimen for Pregnant Women Acute uncomplicated cystitis	Cost per course
Cephalexin	500mg QID x 7 days	$12.60
Nitrofurantoin[1,3] Monohydrate/ Macrocrystals	100mg BID X 5 days **(DO NOT USE In Late 3rd Trimester)**	$7.86
Amoxicillin[2]	500mg TID x 7 days	$7.18
TMP/SMX[3]	1 DS tab BID x 3 days **(DO NOT USE in 1st OR 3rd trimester)**	$0.73

[1] Nitrofurantoin should not be used in patients with CrCl < 30 ml/min.

[2] Should not be used empirically as high resistance rates with *E.coli* and no activity against *Klebsiella.*

[3]Option for patients with penicillin allergy.

Recurrent cystitis

- Recurrence is defined as ≥ 2 uncomplicated, culture positive UTIs in 6 months or ≥ 3 in 12 months.
- If recurrence occurs within ~30 days, obtain a urine culture and rule out pyelonephritis and prostatitis in men.
  - Consider different antibiotic than previous choice, as presence of resistant bacteria is more likely. If previous therapy was a 3-day course, may treat for 7 days.
- If recurrence occurs after ~30 days, consider obtaining a urine culture. The same 1st line empiric antibiotic, as with the initial cystitis episode, is reasonable to use if the person previously responded.
- Consider offering a "delayed prescription" for patients able to recognize symptoms with instructions to start antibiotics upon onset of symptoms. Advise patients to contact prescriber if symptoms do not resolve or improve within 48 hours of starting antibiotics.

ASYMPTOMATIC BACTERIURIA (ASB)

- Asymptomatic bacteriuria (ASB) is the presence of bacteria in the bladder **without symptoms** (dysuria, urgency, frequency, suprapubic pain or tenderness). Therefore, it is **NOT AN INFECTION**.

- ASB is common in
  - long term care residents
    - ≥ 15%-30% of men
    - ≥ 25%-50% of women
  - catheterized patients
  - patients with an abnormal urinary tract

- Screening for or treating ASB with antibiotics is **not recommended** except in pregnancy or prior to invasive genitourinary procedure.
  - Pregnant women should be screened once at the first prenatal visit with urine culture for asymptomatic bacteriuria.
  - The treatment options for pregnant women with UTIs (page 40) apply to the treatment of ASB in pregnancy.
  - It is important to repeat testing at an appropriate interval to check for cure.

- Pyuria accompanying ASB is not an indication for antimicrobial treatment.
  - Pyuria (WBC in the urine) indicates inflammation in the genitourinary tract, but does not differentiate infection from colonization.
  - Positive urine cultures are virtually always associated with pyuria (>90%) and neither is sufficient for a diagnosis of infection.

- A patient with a chronic indwelling catheter will frequently have bacteriuria, but antibiotic treatment is only warranted if symptomatic.

- Changes in the character of the urine such as odor, color, or turbidity are associated with bacteriuria, but are **not** a reliable **predictor** of UTI and are usually due to other reasons, such as incontinence or dehydration.

- Acute symptoms may be difficult to recognize because of impaired communication, dementia, or comorbid illnesses.

- For elderly patients (non-catheterized or catheterized), without localizing urinary tract symptoms, the following signs/symptoms do NOT necessarily warrant investigation or treatment for UTI:
    - Dizziness
    - Increased falls
    - Decreased appetite
    - Altered behavior
    - Confusion/disorientation
    - Before attributing delirium to a UTI, always consider the following conditions:
        - Dehydration
        - New medication/drug interactions
        - Trauma
        - Hypoxia
        - Hypoglycemia
        - Infections other than UTI

SKIN AND SOFT TISSUE INFECTIONS (SSTI)

- SSTIs are classified as uncomplicated (simple) or complicated (necrotizing or non-necrotizing) and can involve the skin (epidermis and dermis), subcutaneous tissue (hypodermis), fascia, and muscle. SSTIs can also be grouped by purulent or non-purulent infections. This guide focuses on uncomplicated SSTIs.

- Predisposing risks for SSTIs include
  - Trauma (laceration, abrasion, shaving injury, bite)
  - Underlying skin condition (ulcer, tinea infections, psoriasis)
  - Vascular disease (peripheral arterial disease, venous stasis)
  - Prior SSTI
  - Lymphedema
  - Saphenous vein harvesting
  - Diabetes, obesity

Red flags for complicated SSTI

- Signs of rapid deterioration, septicemia, shock or confusion
- Rapid onset of severe pain, especially if out of proportion to the clinical findings
- Loss of sensation in the affected area
- Significant periorbital involvement
- Immunosuppression and asplenia
- Animal or human bites
- Progression despite antibiotic use
- Induration, necrosis, hemorrhagic bullae, crepitus

- SSTIs treated in the outpatient setting are typically uncomplicated (no red flags) and limited to skin and subcutaneous tissue involvement.

- <u>Impetigo</u>
  - Involves the epidermis
  - Most common in children aged 2-5
  - Includes **non-bullous impetigo:** Honey-coloured crusted lesions and **bullous impetigo:** fluid-filled vesicles and flaccid bullae

- Pathogens
  - Most commonly group A streptococcus (GAS) and *S. aureus;* Group B, C/G streptococci are less common

- **Management of impetigo**
  - A **topical antibiotic** is **preferred** for impetigo that is limited and localized (i.e. 2-3 small areas).
    - Mupirocin 2% (Bactroban) ointment applied TID (**$17/30g tube,** McKESSON)
    - Fusidic acid 2% (Fucidin) ointment applied TID-QID (**$24/30g tube,** McKESSON)
  - Wash lesions with soap and water to help gently remove crusts
  - Situations indicating the need for a different diagnosis and/or treatment (e.g. oral antibiotics – see page 50) include:
    - Limited or localized infection unresponsive to topical antibiotic after 24-48 hours)
    - Recurrent or widespread infection (numerous or large lesions)

➢ **Erysipelas, Cellulitis, Purulent SSTI**

- <u>Erysipelas</u>
  - Predominately GAS
  - Superficial tissues involved
  - Raised border that is sharply demarcated from the adjacent normal skin
  - Commonly involves the bridge of the nose and cheeks
  - Can be difficult to distinguish from cellulitis

- <u>Cellulitis (without abscess)</u>
  - Involves skin and subcutaneous tissue
  - GAS is the main cause; *S. aureus* is less common.

- <u>Purulent SSTI*</u>
  - Cutaneous abscesses, furuncles, carbuncles
    - **Furuncle**: infection of the hair follicle extending into the subcutaneous tissue.
    - **Carbuncles**: cluster of furuncles, extending deeper into the subcutaneous fat
  - May be associated with surrounding cellulitis

* Purulence: presence of thick and cloudy fluid. This may be draining or contained in an abscess

- Main pathogens
  - MSSA
  - Methicillin-resistant *S. aureus* (MRSA)
    - History of MRSA colonization or infection
    - Recent hospitalization
    - Injection drug use
    - Poor response to initial antibiotic

- **Diagnosis**
  - SSTIs are characterized by heat, pain, tenderness, erythema, swelling and should be differentiated from mimickers:
    - Charcot foot (neuropathic arthropathy)
    - Deep vein thrombosis
    - Erythema migrans (Lyme disease – see page 51)
    - Superficial thrombophlebitis
    - Venous stasis dermatitis
    - Gout
  - Superficial skin swabs are **NOT** recommended unless drainage can be obtained from a purulent lesion by aspiration or puncture. Aspiration from non-purulent cellulitis is not recommended.

- **Classification**
  - Various classification schemes have been developed to assist the clinician in deciding the severity of the infection and the most appropriate therapy.
    - None of these schemes has been validated and they are meant for general guidance only. For example, not every immune compromised patient has a severe SSTI and some patients with mild systemic signs might go on to develop a severe infection if the diagnosis and treatment are delayed.
    - The numbered classification scheme offers additional clinical variables that might assist in coming to the more accurate diagnosis.

Mild	Moderate	Severe
• No systemic signs of infection	• Systemic signs of infection	• SIRS* • Failed oral antibiotic therapy • Immunocompromise • Deep infection: bullae, skin sloughing, or end organ dysfunction

*Temp >38°C, respiratory rate >24 breaths per min, heart rate > 90 beats per min, WBC >12 or <4

Class 1

- Afebrile, no systemic symptoms or sepsis

Class 2

a) Systemic symptoms: fever, chills lymphangitis &/or rapidly advancing edge
b) Class 1 with comorbidity*

Class 3

a) Toxic and unwell¶
b) Failure to respond to >48 h of adequate oral antibiotics
c) Severe facial or extensive extremity involvement
d) High risk patients**

Class 4

a) Septic shock

b) Life-threatening infection, e.g. necrotizing fasciitis, orbital, joint, or deep hand involvement

* Peripheral vascular disease, diabetes, chronic venous insufficiency, morbid obesity, chronic lymphedema

¶ Mental status changes, tachycardia, tachypnea or hypotension

**High risk patients: neutropenia, asplenia, active cancer and/or chemotherapy, morbid obesity, autoimmune diseases, transplant, prosthetic joint or valve, HIV with CD4 count <200

- **Cellulitis/Erysipelas:**

Cellulitis/Erysipelas		
Antibiotic	**Adult regimen**	**Cost per day**
MILD (Class 1, some Class 2*)		
Penicillin VK[1]	300-600mg PO QID	$0.81 - $1.62
Cephalexin	500mg PO QID	$1.80
Cefuroxime[2]	500mg PO BID	$2.86
Clindamycin[3]	300-450mg PO QID	$1.88 - $2.82
MODERATE (Class 2* or 3)		
Cefazolin[2,4]	**Inpatient:** 2g IV q8h **Outpatient:** 2g IV q12h & 1 g probenecid PO 30min before	$24.00
Cloxacillin[4]	2g IV q4h	$54.86
Ceftriaxone[4]	1g IV q24h	$12.49
Vancomycin[3,4]	15mg/kg IV q12h	$219.32/75 kg
Duration of therapy 5 days if mild and quick response, otherwise 7-10 days		
SEVERE (Class 4)		
Immediate expert consultation		
Broad spectrum antimicrobials		

[1] If erysipelas clinically established, does not cover MSSA

[2] 1st line empiric therapy if patient has IgE mediated penicillin allergy

[3] Option if unable to use any β-lactam

[4] Can transition to oral therapy when systemic symptoms resolved for >24 hours

*Oral or parenteral antibiotics may be used depending on the clinical scenario. Clinical judgment required.

- **Purulent SSTI (Cutaneous abscesses, Furuncles, Carbuncles)**
  - **Incision and drainage** (I & D) is the cornerstone of management and may be sufficient for clinical cure in mild, uncomplicated cases.
  - Hot compresses are recommended for furuncles, carbuncles.
  - Antibiotics do not replace the need for incision and drainage.

	Purulent SSTI (Cutaneous abscesses, Furuncles, Carbuncles) NO MRSA CONCERNS		
	Antibiotic	**Adult regimen**	**Cost per day**
I & D	MILD (Class 1)		
	No antibiotics required		
	MILD (Class 1) with abscess diameter >2 cm or other INDICATION for antibiotic[1] or some Class 2*		
	Cephalexin	500mg QID	$1.80
	TMP-SMX[3]	1-2 DS tabs PO BID	$0.24 - $0.48
	Doxycycline[3]	200mg 1st dose then 100mg PO BID	$1.17
	Clindamycin[3]	300-450mg PO QID	$1.88 - $2.82
	MODERATE (Class 2* – 3)		
	Cefazolin[2,4]	**Inpatient:** 2g IV q8h **Outpatient:** 2g IV q12h & 1 g probenecid PO 30min before	$24.00
	Vancomycin[3,4]	15mg/kg IV q12hr	$219.32/75 kg
	Duration of therapy 7-10 days		
	SEVERE (Class 4)		
	Immediate expert consultation		
	Broad spectrum antibiotics		

	Purulent SSTI (Cutaneous abscesses, Furuncles, Carbuncles) MRSA CONCERNS		
	▪ History of MRSA colonization or infection ▪ Recent hospitalization ▪ Injection drug use ▪ Poor response to initial antibiotics		
	Antibiotic	**Adult regimen**	**Cost per day**
I & D	MILD (Class 1)		
	No antibiotics required		
	MILD (Class 1) with abscess diameter > 2 cm or other INDICATION for antibiotic[1] or some Class 2*		
	TMP-SMX	1-2 DS tabs PO BID	$0.24 - $0.48
	Doxycycline	200mg 1st dose then 100mg PO BID	$1.17
	Clindamycin[5]	300-450mg PO QID	$1.88 - $2.82
	MODERATE (Class 2* – 3)		
	Vancomycin[4]	15mg/kg IV q12hr	$219.32/75 kg
	Duration of therapy 7-10 days		
	SEVERE (Class 4)		
	Immediate expert consultation		
	Broad spectrum antibiotics		

[1] May add antibiotic therapy if
- Multiple abscesses
- Lack of response to incision and drainage alone
- Extensive surrounding cellulitis
- Located in an area where incision and drainage difficult (face, hands or groin)
- Extremes of age
- Impaired host defenses
- Indwelling medical device at a non-contiguous site, isolated from infected field (e.g. pacemaker, vascular graft)

[2] 1st line empiric therapy if penicillin allergy (IgE mediated)
[3] Options if unable to use any β-lactam
[4] Can transition to oral therapy when systemic symptoms resolved for >24 hours
[5] Clindamycin remains a reasonable option for community-acquired MRSA which are more susceptible than hospital-acquired MRSA strains. Of 58 isolates tested across Canada, 88% were sensitive in 2015. Current local susceptibilities to TMP-SMX and doxycycline are 93% and 100% respectively.
*Oral or parenteral antibiotics may be used depending on the clinical scenario. Clinical judgment required.

- **Treatment considerations**
  - Visible improvement of clinical manifestations may take up to 72 hours, erythema and extension often progress in first 24 hours of treatment. (pain often gets better even if visible erythema is not)
  - Systemic symptoms (if present) usually improve in 24-48 hours if on appropriate treatment

- Residual skin discoloration or defect may be present at end of antibiotic course. Full skin healing may take at least an additional 1-2 weeks.
- Residual limb edema may persist for several weeks/months after other signs of infection resolve.
- Oral cloxacillin is poorly absorbed and tolerated so it should not be used.

- **Adjuvant management recommendations**
  - **Elevation** of the affected area (above level of heart for majority of the day) is **essential.**
  - The skin should be sufficiently hydrated to avoid dryness and cracking without interdigital maceration.
  - Treat underlying conditions (i.e. tinea pedis)
  - Blood cultures if systemic symptoms
  - Assess vascular supply if suspicion of arterial insufficiency (i.e. ABI)
  - Long-term management of chronic venous insufficiency and chronic lymphedema with compression

Antibiotic	Pediatric SSTI regimen	Cost per kg per day
Cephalexin[1]	50 mg/kg/day Divided QID Maximum 4000 mg/day	$0.57
TMP/SMX[4,5]	8-12mg/kg/day Divided BID Based on trimethoprim component	$0.20 – 0.30
Clindamycin[6]	20 mg/kg/day Divided TID Maximum 1800 mg/day	$0.27
Duration of therapy 5 days if mild and quick response, otherwise 7-10 days		

[1] 1st line empiric therapy for GAS and MSSA

[4] 1st line empiric therapy for Community acquired- methicillin resistant *S. aureus* (CA-MRSA) MSSA if penicillin allergy (IgE mediated) or severe non-IgE mediated reaction to penicillin

[5] Does not cover GAS

[6] 1st line empiric therapy for GAS if unable to take any β-lactam

LYME DISEASE

- Lyme disease is a tick-borne infectious disease caused by different species of *Borrelia.*
  - In Canada, Lyme disease is caused by *Borrelia burgdorferi* and is transmitted by infected ticks.
    - *Ixodes scapularis* (black legged ticks) in central and eastern Canada
    - *Ixodes pacificus* (western blacklegged ticks) in western Canada
  - In Europe and Asia, Lyme disease is transmitted by other species of *Borrelia.*

- This document will focus only on the role of antibiotics in the **treatment** of early Lyme disease. Please refer to selected references and websites.
  - In Nova Scotia, the Infectious Diseases Expert Group (IDEG) of the Department of Health and Wellness have issued a "Statement for Managing Lyme Disease in Nova Scotia".
    - The Statement endorses the Infectious Diseases Society of America (IDSA) guidelines (2006) which are currently being updated.
    - Please refer to https://novascotia.ca/dhw/cdpc/documents/statement_for_managing_LD.pdf

- The likelihood of transmission of *B. burgdorferi* is extremely low if attachment is < 36 hours and the tick is not engorged. Monitoring the patient for 30 days is suggested.

- Although patients with *B. burgdorferi* infection can be asymptomatic, most cases of Lyme disease present as one of 3 stages. These may occur sequentially if an earlier stage is untreated.
  - Early localized disease (usually < 30 days from exposure)
    - Generally presents within 7-14 days, up to 30 days
    - 70-80% of patients present with a classic erythema migrans rash which consists of a single erythematous, expanding, > 5 cm rash +/- central clearing at the site of the tick bite.
  - Early disseminated disease (< 3 months after exposure)
  - Late disseminated disease (> 3 months after exposure)

- The treatment of Lyme disease depends on the stage and organ systems involved.
  - For complete details, please refer the Nova Scotia statement (link above) or to the review of diagnosis and treatment of Lyme Disease in the Canada Communicable Disease Report (CCDR) available at https://doi.org/10.14745/ccdr.v40i11a01
  - For children, also refer to the SPECTRUM app at http://www.spectrum.md/iwk/

Table 6: Guidelines for treatment of early localized Lyme disease (OFF LABEL USE)

ADULTS (IDSA)		
Manifestation	**Antibiotic**	**Cost per day**
Erythema migrans or early disseminated disease, including Bell's palsy, but **without** other CNS involvement	➢ Doxycycline 100 mg po BID x 14-21 days (contraindicated in pregnancy)	$1.17
	➢ Amoxicillin 500 mg po TID x 14-21 days	$1.02
	➢ For penicillin allergy Cefuroxime 500 mg po BID x 14-21 days	$2.86
CHILDREN 8 years and older (SPECTRUM)		
Early localized disease Cutaneous disease- Erythema migrans(single or multiple) only	➢ Doxycycline 4.4 mg/kg/day po divided BID x 10 days. Round dose to nearest 25 mg (1/4 tablet) (maximum 200 mg/day) For isolated facial palsy, give for 14 days	$0.59
CHILDREN less than 8 YEARS (SPECTRUM)		
Early localized disease Cutaneous disease- Erythema migrans (single or multiple) only	➢ Amoxicillin 50 mg/kg/day, po divided TID x 14 days (maximum 1500 mg/day)	$0.05
	➢ For penicillin allergy Cefuroxime 30 mg/kg/day, po divided BID x 14 days (Maximum 1000 mg/day)	$0.23

- In Nova Scotia, the Infectious Diseases Expert Group (IDEG) **recommends AGAINST prolonged courses** of antimicrobials for the **treatment of Lyme disease** that are not in keeping with courses recommended by the IDSA treatment guidelines.
- In Nova Scotia, prophylaxis is generally not recommended. It may be offered to patients who meet all of the following criteria:
  - Attached tick reliably identified as *I. scapularis*
  - Tick is estimated to have been attached for > 36 hours on the basis of the degree of engorgement or by certainty about time of tick attachment
  - Prophylaxis can be started within 72 hours of tick removal
  - Local rate of *B. burgdorferi* infection in ticks is > 20% (Currently not reported in Nova Scotia)
  - Doxycycline is not contraindicated

Table 7: Prophylaxis for Lyme Disease (CCDR 2014)

Antibiotic	Prophylaxis adults and children ≥ 8 years Lyme Disease	Cost
Doxycycline	Adults: 200 mg for 1 dose Children: 4.4 mg/kg maximum dose of 200 mg (Round dose to nearest 25 mg (1/4 tablet)	$0.59
Contraindicated in pregnancy and children < 8 years old		

- Evidence on the efficacy of prophylaxis was reviewed in a 2010 systematic review and meta-analysis. (J Antimicrob Chemther 2010; 65:1137 – 1144)
  - The review and meta-analysis included 4 RCTs (N= 1082) and enrolled patients within 72 hours of tick bite. One of the included RCTs evaluated single dose doxycycline. Results of the review and meta-analysis are summarized below.

Outcome	Event Rate		ARR	NNT (95% CI)
	Antibiotic	Placebo		
Lyme Disease	0.2%	2.2%	2%	50 (45-106)

  - However, if prophylaxis was restricted to patients whose ticks were visibly engorged, the NNT becomes 11 (95% CI 10 to 25).
- The use of a single dose of doxycycline as prophylaxis for the prevention of Lyme disease was evaluated in a 2001 RCT. (NEJM 2001; 345(2): 79-83)
  - The trial enrolled 482 subjects who had removed attached *I.scapularis* ticks within the previous 72 hours.
    - Event rate in the placebo group is 3.2%.

Outcome	Event Rate		ARR	NNT (95% CI)
	Doxycycline	Placebo		
Erythema migrans	0.4%	3.2%	2.8%	36 (95% CI not available)

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