Antibiotics & Common Infections
Stewardship, Effectiveness, Safety & Clinical Pearls
October 2016

ANTIMICROBIAL RELATED LINKS

CANADIAN GUIDELINES
Bugs & Drugs (Alberta/BC): http://www.bugsanddrugs.ca/

PATIENT RESOURCES
Canadian Antibiotic Awareness: http://www.antibioticawareness.ca
which includes:
1. Viral Prescription Pad for respiratory infections (download or order for free), provides information about symptomatic relief for viral infections and indicates when patients should consider a return visit.
2. Talking with Patients about When to Use Antibiotics provides communication tips to effectively address requests for antibiotics for viral infections.

Enhanced communication skills reduce antibiotic prescribing (27% absolute risk reduction - ARR).

3. Posters for office A poster displayed in the practice waiting room stating a commitment to reducing antibiotic use reduces inappropriate antibiotic use (20% ARR).


OTHER
www.rqhealth.ca/antimicrobialstewardship
For more public/patient resource links see: www.RxFiles.ca/ABX

ANTIMICROBIAL STEWARDSHIP

There are world-wide efforts that look for strategies to deal with the challenge of growing antimicrobial resistance. How can we all work together to be stewards of this important, but limited resource?

SELECT ANTIBIOTIC RESISTANT PATHOGENS OF MAJOR CONCERN

- methicillin-resistant Staphylococcus aureus (MRSA)
- multi-drug resistant Streptococcus pneumoniae (MRSP)
- vancomycin-resistant enterococci (VRE)
- multi-drug resistant Escherichia coli & other gram negative bacteria (e.g. ESBL)

KEY STRATEGIES FOR REDUCING ANTIBIOTICS

- vaccinations to prevent infections and decrease antibiotic use
- practice and educate on infection prevention (wash hands, avoid touching eyes, cough etiquette, stay home when sick)
- avoid antibiotics for infections of predominantly viral cause
- use of point-of-care tools/tests
- treat infection, not contamination
- avoid treating positive cultures in the absence of signs/symptoms

STRATEGIES WHEN ANTIBIOTICS INDICATED

- Whenever suitable:
  - use narrow-spectrum agent
  - use shorter duration therapy
  - tailor empiric antibiotic choice & dosage according to local bacterial prevalence and resistance patterns
  - calculate weight-based dose in kids
  - if patient experiences an adverse reaction, provide patient education and document details to avoid labelling a side effect as an "allergy"
  - discourage saving of "left-over" antibiotics for future use

GETTING STRATEGIES TO WORK - REAL WORLD

- Public, patient & provider education over time to change expectations
- Realistic appreciation for viral versus bacterial etiologies
- Delayed prescriptions for select conditions with instructions to fill only if symptoms do not resolve or condition worsens. (Offer to those who value convenience.)
- “It’s easy to prescribe antibiotics. It takes time, energy & trust not to do so.”

Success lies in changing the culture & the understanding of antibiotic limitations, benefits & harms.

ANTIBIOTIC HARMs – UNDERAPPRECIATED

- To the Patient
  - 1 in 5 emergency room visits for adverse drug events (ADEs) are from antibiotics.
  - Antibiotics are the most common cause of ADEs in children, accounting for 7 of the top 15 drugs leading to ADE-related ER visits.
  - Antibiotic associated diarrhea, including Clostridium difficile diarrhea
  - Cardiac - QT interactions: with clarithromycin & fluoroquinolones
  - Central nervous system (CNS) adverse effects (e.g. dizziness, headache, sleep disturbance, seizure, encephalopathy)
  - Hyperkalemia (cotrimoxazole)
  - Skin: minor/major (e.g. cotrimoxazole)
  - Tendon rupture (fluoroquinolones)
  - Risk of drug interactions (warfarin, statins/macrolides, ...)

- To Society
  - financial costs of treating adverse reactions (USA: $20 billion in excess healthcare costs)
  - antimicrobial resistance: more difficult to treat infections over time, leading eventually to no adequate options

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Antibiotics & Common Infections – Part 1

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<td>Nitrofurantoin</td>
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<tr>
<td>Fosfomycin</td>
<td></td>
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<tr>
<td>Linezolid</td>
<td></td>
</tr>
<tr>
<td>Probenecid (used to prolong effective levels of cefazolin)</td>
<td></td>
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<tr>
<td>Vancomycin</td>
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Coming up next, Spring 2017

ABX – Part 2:
Skin Infections, Acute Cystitis

www.RxFiles.ca

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PEARLS for the MANAGEMENT of ACUTE UNCOMPLICATED BRONCHITIS

- Antibiotics are NOT recommended, as bronchitis is predominantly viral.
- Arrange on treatments that will provide symptomatic relief: maintaining hydration & ↑ humidity. Cough suppressants may be considered for managing cough, & inhaled bronchodilators if wheezing is present. Honey may help children.
- Patients should see their prescriber if: 1) symptoms worsen, 2) new symptoms develop (e.g. dyspnea, fever, vomiting), 3) cough >1month, or 4) >3 episodes/yr.

SYMPTOM MANAGEMENT

<table>
<thead>
<tr>
<th>NONPHARM</th>
<th>No quality evidence, but anecdotally may help</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑/maintain hydration</td>
<td>No evidence for or against.</td>
</tr>
<tr>
<td>↑ humidity (e.g. PRN humidifier to maintain 30-50% humidity)</td>
<td>- Hydration: caution in HF &amp; CKD patients</td>
</tr>
<tr>
<td>Honey 2.5 to 10mL po qHS Not recommended in &lt;1yr due to concerns with infant botulism</td>
<td>- No strong evidence for or against.</td>
</tr>
<tr>
<td>Dextromethorphan (DM) e.g. BENYLIN DM, ROBITUSIN DM 10-30mg po q6-8hr PRN</td>
<td>- Cochrane review (3 RCTs, n=568): better than placebo, but inferior to dextromethorphan in cough frequency (cough duration not assessed).</td>
</tr>
<tr>
<td>Salbutamol VENTOLIN 100mcg 2 puffs inhaled QID</td>
<td>- May ↓ number of coughing episodes but does not ↓ duration of illness.</td>
</tr>
<tr>
<td>Ipratropium ATROVENT 20mcg 4 puffs QID</td>
<td>- Not recommended in children under 6 years of age due to safety &amp; efficacy concerns.</td>
</tr>
</tbody>
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PRE-TREATMENT CONSIDERATIONS

- Inappropriate antibiotic use is driving resistance & leading to a crisis. Please examine your own prescribing practices. Refer to newsletter cover.
- The majority of acute uncomplicated bronchitis cases are viral (90% in adults & 95-100% in children).
- Antibiotics are NOT recommended for acute uncomplicated bronchitis. Several RCTs assessing the efficacy of antibiotics for this indication have failed to show a benefit; however, up to 80% of adults in the U.S. still receive an antibiotic.
- Acute uncomplicated bronchitis is self-limiting. Cough usually persists for 1 to 3 weeks, although up to 50% of viral cases will have a cough beyond 3 weeks. Airway hyperactivity may last up to 6 weeks. Recommend symptom management.
- Acute complicated bronchitis (e.g. history of smoking, impaired lung function, chronic heart disease, immunocompromised) may require further investigation (e.g. lung function tests, chest x-ray).
- Rule out pneumonia if the following signs are present: HR>100bpm, RR >24 breaths/min, oral temperature >38°C, or findings of local consolidation.
- Coloured sputum does not reliably differentiate between bacterial or viral origin.
- Fever is uncommon, & may be indicative of influenza or pneumonia.
- If the patient has confirmed pertussis, see RxFiles pg 78 for antibiotic regimens. Uncommon, but there is the occasional outbreak. Encourage vaccination.

COUGH SUPPRESSANTS

- May improve daytime & nighttime cough, & dyspnea associated with coughing.

BRONCHODILATORS

- Limited evidence (1 study with fenoterol, n=80).
- May ↓ duration of cough in patients with wheezing/airflow obstruction when used x 1wk (NNT=2, NNH=2 for tremor, shakiness, nervousness).

- Limited evidence (1 study, n = 14 for 3 weeks) in post-infectious cough.
- Expectorants (e.g. guaifenesin): most evidence failed to show a benefit.

- Not routinely recommended for symptom management:
  × Oral or inhaled corticosteroids are not recommended in patients with acute bronchitis without asthma.
  × Expectorants (e.g. guaifenesin): most evidence failed to show a benefit.

Clinical Q&A

Should pts ≥ 65yrs be treated with an ABX to ↓ the risk of developing pneumonia?
- No, but patients presenting with signs of pneumonia should undergo investigation (e.g. chest x-ray).
- A previous retrospective cohort study (1991 to 2001) suggested that individuals with acute bronchitis who were ≥65 years may benefit from antibiotics (NNT to prevent 1 additional case of pneumonia in the month following acute bronchitis was 39 for those ≥65 years, & 199 for those between 16-64 years of age).
- However, a 2013 RCT (n=1,038) comparing amoxicillin 1000mg po TID x 7 days to placebo showed no difference in duration or severity of symptoms up to 1 month, regardless of age. There was an ↑ risk of adverse events (nausea, rash, diarrhea) with the amoxicillin group (NNH=22).

Abbreviations: ABX=antibiotic CKD=chronic kidney disease HF=heart failure NNH=number needed to harm NNT=number needed to treat RCT=randomized controlled trials TMP-SMX=trimethoprim/sulfamethoxazole

MOST COMMON PATHOGENS

- Viral – e.g. Influenza A, Influenza B, Parainfluenza, RSV, & Adenovirus

EMPIRIC DRUG REGIMENS OF CHOICE & SUSCEPTIBILITY CONCERNS

- Antibiotics are not recommended for acute uncomplicated bronchitis.
- Multiple studies & meta-analyses assessing antibiotics for the treatment of acute uncomplicated bronchitis have shown no benefit or modest improvement, along with an ↑ risk of adverse events.
- For example, a 2014 Cochrane review (17 RCTs, n=3,936) evaluating antibiotics (beta-lactams, doxycycline, macrolides, TMP-SMX) vs placebo found no difference in clinical improvement. Antibiotics ↓ cough (NNT=6), night cough (NNT=7) & mean duration of cough by 0.5 days, but ↑ risk of adverse events (NNH=5, primarily gastrointestinal related).
COMMUNITY ACQUIRED PNEUMONIA: Management Considerations

**PEARLS for the MANAGEMENT of COMMUNITY ACQUIRED PNEUMONIA (CAP)**

- A chest x-ray is recommended to confirm suspected pneumonia.  
  IDSA/07 LOE: moderate
- The CRB-65 score can be used to help identify adults who may require hospital admission due to a higher risk of mortality.
- **S. pneumoniae** is the most common bacteria, even in those with comorbidities.
- **Doxycycline** covers the majority of bacterial CAP pathogens (e.g. **S. pneumoniae**, **S. aureus**, **H. influenzae** & atypicals). Standard duration of therapy is **5 to 7 days**.
- There is limited data on the role of **corticosteroids** in outpatients.
- Recommend the influenza vaccine every fall.
- Recommend the pneumococcal vaccine x1 for those ≥65 years of age, or at high risk regardless of age (e.g. chronic cardiac or pulmonary disease, DM, CKD).
- Patients should see their prescriber if symptoms worsen or do not improve within 48-72 hours. Cough, fatigue or dyspnea may persist for up to 1 month, or longer.

**PRE-TREATMENT CONSIDERATIONS**

- A chest x-ray is the most accurate way to diagnose CAP, regardless of age.
- Despite challenges with obtaining a good specimen, a sputum C&S will help differentiate between bacterial versus viral CAP. It can also help identify patients who may require broader spectrum antibiotics.
- Rule out influenza during late fall/early spring; consider a nasopharyngeal swab.
- Review antibiotics associated with higher **S. pneumoniae** resistance prescribed over the past 3 months. May warrant using an agent from another antibiotic class.

**OUTPATIENT vs HOSPITAL ADMISSION**

- Several severity of illness scores are available for pneumonia (see RxFiles page 90).
- **Adult Outpatients**: the CRB-65 does not require any blood work & can be easily used in an office setting to identify patients who may require hospital admission.

<table>
<thead>
<tr>
<th>CRB-65 Criteria</th>
<th>Points</th>
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<tbody>
<tr>
<td>Confusion: new onset based on a specific mental test, or disorientation to person, place or time</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory rate ≥30 breaths/minute</td>
<td>1</td>
</tr>
<tr>
<td>Low Blood pressure: SBP &lt;90mmHg or DBP ≤60mmHg</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>1</td>
</tr>
</tbody>
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- Score | Risk of Mortality | Suggested Management |
<table>
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<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt; 2%</td>
<td>Outpatient</td>
</tr>
<tr>
<td>1-2</td>
<td>~9%</td>
<td>Consider hospital admission</td>
</tr>
<tr>
<td>≥3</td>
<td>&gt;19%</td>
<td>Hospital admission</td>
</tr>
</tbody>
</table>

If a recent ura is available, may use CURB-65 where BUN >7mmol/L = 1 point. See RxFiles page 90 for information on LTC and pediatric patients.

**EMPIRIC DRUG REGIMENS OF CHOICE**

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<tr>
<th>PREVIOUSLY HEALTHY ADULT OUTPATIENT WITH NO RECENT ANTIBIOTIC USE</th>
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<tr>
<td>Most Common Bacterial Pathogen: Gram +ve: <strong>Streptococcus pneumoniae</strong></td>
</tr>
<tr>
<td>Potential Pathogens: Atypical pathogens (<strong>M. pneumoniae</strong>, <strong>C. pneumoniae</strong>)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Regimen</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Doxycycline</strong></td>
<td>200mg po Day 1, then 100mg po BID x 5-7 days</td>
<td>Based on SK antibiogram data RQHR, SDCL, SHR, doxycycline has good activity against common/potential CAP pathogens (i.e. <strong>S. pneumoniae</strong> &amp; atypical pathogens).</td>
</tr>
<tr>
<td><strong>Amoxicillin</strong></td>
<td>1000mg po TID x 5-7 days</td>
<td><strong>S. pneumoniae</strong> (even intermediate susceptibility isolates) remain sensitive to high-dose amoxicillin.</td>
</tr>
<tr>
<td><strong>Clarithromycin</strong></td>
<td>may consider adding a macrolide if concerned about atypical pathogens (see Clinical Q&amp;A)</td>
<td><strong>S. pneumoniae</strong></td>
</tr>
<tr>
<td><strong>Azithromycin</strong></td>
<td>500mg po daily x 3 days, or 1000mg po daily x 5-7 days</td>
<td><strong>S. pneumoniae</strong></td>
</tr>
</tbody>
</table>

**ADULT OUTPATIENT with COMORBIDITIES / ABX RESISTANT RISK FACTORS**

<table>
<thead>
<tr>
<th>Most Common Bacterial Pathogen: Gram +ve: <strong>S. pneumoniae</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential Pathogens: <strong>H. influenza, M. catarrhalis, K. pneumoniae</strong></td>
</tr>
<tr>
<td>Atypical pathogens: <strong>M. pneumoniae</strong>, <strong>C. pneumoniae</strong>, <strong>Legionella</strong></td>
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<tr>
<th>Drug</th>
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<tr>
<td><strong>Doxycycline</strong></td>
<td>200mg po Day 1, then 100mg po BID x 5-7 days</td>
<td>As above, &amp; will also cover <strong>S. aureus</strong> &amp; potential gram –ve pathogens.</td>
</tr>
<tr>
<td><strong>Amoxicillin - Clavulanate</strong></td>
<td>875mg po BID x 5-7 days</td>
<td><strong>S. pneumoniae</strong></td>
</tr>
<tr>
<td><strong>Amoxicillin</strong></td>
<td>may consider adding a macrolide re: atypical pathogens (see Clinical Q&amp;A)</td>
<td><strong>S. pneumoniae</strong></td>
</tr>
<tr>
<td><strong>Fluoroquinolones should be reserved</strong></td>
<td>for treatment failures, comorbidities with recent antibiotic use, allergies or documented infections with highly drug-resistant bacteria. Examples: levofloxacin <strong>LEVAQUIN</strong> 500-750 mg po once daily x 5 days, moxifloxacin <strong>AVELOX</strong> 400 mg po once daily x 5 days</td>
<td><strong>S. pneumoniae</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CRB-65</th>
<th>Score</th>
<th>Risk of Mortality</th>
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<td>&gt;19%</td>
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*Comorbidity or risk factor for ABX-resistant **S.pneumoniae**: age ≥65, cardiac, pulmonary, renal or hepatic failure; smoking; alcoholism; malignancy; DM; malnutrition or acute weight loss (>5%); immunosuppressive tx including corticosteroid use (high-dose >30 mg); hospitalization or broad spectrum ABX in past 3 months; HIV/Immunosuppressed.

COMMUNITY ACQUIRED PNEUMONIA: Management Considerations

**Duration of Therapy in Adults:**
- **Treat for a minimum of 5 days & until afebrile for 48-72hrs.**
- **Meta-analyses (15 RCTs n=2,796; 5 RCTs n=1,303)** comparing treatment durations of ≤7 days to >7 days showed no difference in clinical success rates in ambulatory pts.
- **Azithromycin 3 vs 5 days:** limited data is available comparing the two regimens, but there does not appear to be a difference in efficacy or safety. Due to the long t½ (~68 hours in adults), a 3-day course of azithromycin is in essence providing therapy beyond 3 days. Patients may still feel unwell at Day 3; reassure ABX is still working.

**Doxycycline as a 1st line agent**
- Meta-analyses (15 RCTs n=2,796; 5 RCTs n=1,303) comparing treatment durations of ≤7 days to >7 days showed no difference in clinical success rates in ambulatory pts.
- Although some Canadian references suggest the option of combining doxycycline with a beta-lactam due to concerns with doxycycline resistance to *S. pneumoniae*. Currently, *S. pneumoniae* has good susceptibility to doxycycline in Saskatchewan, & therefore the combination is not necessary.
- **Most guidelines suggest a BID (200mg Day 1, then 100mg BID) regimen**; however 100mg po BID Day 1 followed by 100 mg daily may be suggested due to its long-half life (12hr after first dose, 24hr with multiple doses). Data comparing the efficacy of the two regimens is limited. Anecdotally, twice daily is generally tolerable.

**Duration of Therapy in Pediatrics:**
- **Infants & pre-school children:** viruses are the predominant cause - due to vaccination, typed H. influenzae as a causative pathogen is very rare.
- **>5 years:** *M. pneumoniae, C. pneumoniae*

### Most Common Pathogens:
- **Infants & pre-school children:** viruses are the predominant cause - due to vaccination, typed H. influenzae as a causative pathogen is very rare
- **>5 years:** *M. pneumoniae, C. pneumoniae*

#### FIRST LINE
- **Amoxicillin:** 40-90mg/kg/day po ÷ TID (max 4g/day) x 7 - 10 days
- **Cefuroxime OR Cefprozil:** 20-30mg/kg/day po ÷ BID x 7-10 days (max 500mg/dose) 15-30mg/kg/day po ÷ BID x 7-10 days (max 500mg/dose)
- **Doxycycline:** ≥9 yrs: 4mg/kg/day po ÷ BID (max 200mg/day) x 7 - 10 days
- **Azithromycin safety in <6 months is unknown:** 10mg/kg po Day 1 (max 500 mg/dose), then 5mg/kg po daily x 4 days (max 250mg/day)
- **Clarithromycin safety in <6 months is unknown:** 15mg/kg/day po ÷ BID x 7 - 10 days (max 500mg/dose)

#### PENICILLIN ALLERGY: TYPE IV HYPERSENSITIVITY (e.g. rash)
- **Cefuroxime OR Cefprozil:** Provides coverage for intermediate penicillin-resistant *S. pneumoniae*. Treatment failure not significantly different compared to amoxicillin.

#### PENICILLIN ALLERGY: TYPE I HYPERSENSITIVITY (i.e. anaphylaxis)
- **Doxycycline:** ≥9 yrs: 4mg/kg/day po ÷ BID (max 200mg/day) x 7 - 10 days
- **Azithromycin:** It is difficult for pediatric patients to produce a sputum sample. The majority of respiratory isolates are from tracheal suction & antibiogram data likely does not represent pediatric outpatient.
- **Clarithromycin:** If symptoms worsen or do not improve within 3-5 days, consider adding clindamycin (20-40mg/kg/day po ÷ TID).

**TREATMENT EVIDENCE SUMMARY – ADULT CAP**

**Doxycycline as a 1st line agent**
- Limited evidence with doxycycline for CAP. However, it has *S. pneumoniae, H. influenzae, S. aureus* & atypical coverage; achieves high serum & lung drug concentrations; and has concentration dependent killing.
- Monotherapy sufficient for most, although some Canadian references suggest the option of combining doxycycline with a beta-lactam due to concerns with doxycycline resistance to *S. pneumoniae*. Currently, *S. pneumoniae* has good susceptibility to doxycycline in Saskatchewan, & therefore the combination is not necessary.
- **Most guidelines suggest a BID (200mg Day 1, then 100mg BID) regimen**; however 100mg po BID Day 1 followed by 100 mg daily may be suggested due to its long-half life (12hr after first dose, 24hr with multiple doses). Data comparing the efficacy of the two regimens is limited. Anecdotally, twice daily is generally tolerable.

**Vaccinations:**
- **Recommend an annual influenza vaccine**, as this can ↓ the relative risk of pneumonia by 53%, hospitalization by 50% & mortality by up to 68% observational data, in those age ≥65. Provides best coverage of all beta-lactams against *S. pneumoniae* & *penicillin-resistant strains*. As such, high-dose should be used in RQHR.
- **Recommend a PNEUMOVAX-23 vaccine** for those ≥65 years of age, or at high risk (e.g. DM, CKD, chronic cardiac or pulmonary disease, LTC resident, immunocompromised).- Over a 2 year period, PNEUMOVAX-23 prevents 1 case of pneumonia for every 12 immunized LTC residents.
- **PREVNAR-13** studies showed a ↓ in invasive pneumococcal disease, but not overall pneumonia rates.
- **Neither vaccine type has been shown to provide protection against other atypical pathogens** such as *M. pneumoniae*, *C. pneumoniae*, or *atypical mycobacteria*. As such, these vaccines are not necessarily recommended for all patients.

**Clinical Q&A**

**When is coverage for atypical pathogens needed?**
- Atypicals are thought to be responsible for ~15% of CAP, & maybe more common in the following populations:
  - *M. pneumoniae* in young, healthy adults (CAP usually resolves without ABX)
  - *C. pneumoniae* in LTC residents, immunocompromised patients, or those with multiple comorbidities. Acute onset of symptoms unlikely.
- The role of ABX with atypical coverage in other adults is uncertain. **CAP-START was a non-inferiority study comparing a beta-lactam ± a macrolide for atypical pathogen coverage, or a fluoroquinolone, in 2283 patients in the Netherlands. Median: age 70 years, CURB-65 score=1. ~40% COPD/asthma, ~20% CVD, ~15% DM. Beta-lactam monotherapy was non-inferior to the other 2 treatment arms for the primary endpoint (all-cause mortality).**
- If ABX with atypical coverage is not initiated empirically, consider adding atypical coverage (e.g. add a macrolide to amoxicillin / amox-clav, or switch to doxycycline) if the patient does not improve in 3-5 days or symptoms worsen.
**PEARLS for the MANAGEMENT of PHARYNGITIS**

- The majority of pharyngitis cases do **NOT** require antibiotics as they are viral infections (80-90% in adults, >70% in children).
- Pharyngitis is typically self-limiting (often 3-7 days; up to ≤10 days).
- A validated clinical decision rule e.g. modified Centor score can help identify low risk patients who do not require diagnostic testing (see below) or antibiotics.
- For confirmed Group A Streptococcus (GAS) pharyngitis, penicillin for 10 days is the drug of choice. There is no documented GAS resistance to penicillin.
- Advise on treatments that will provide **symptomatic relief**: NSAIDs, acetaminophen, medicated throat lozenges, topical anesthetics, warm liquids.
- Patients should see their prescriber if: 1) symptoms worsen, 2) symptoms take longer than 3 to 5 days to resolve, 3) unilateral neck swelling develops.

**PRE-TREATMENT CONSIDERATIONS**

- Inappropriate antibiotic use is driving resistance & leading to a crisis. Please examine your own prescribing practices. Refer to newsletter cover.
- A validated clinical decision rule, like the modified Centor score, can be used to help identify low risk patients who do not require diagnostic testing or antibiotics.

**Modified Centor (or McIsaac) Score**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature &gt; 38°C (&gt;100.5°F) oral temperature used in Centor score (adults)</td>
<td>1</td>
</tr>
<tr>
<td>Absence of cough</td>
<td>1</td>
</tr>
<tr>
<td>Swollen, tender anterior cervical nodes</td>
<td>1</td>
</tr>
<tr>
<td>Tonsillar swelling or exudate</td>
<td>1</td>
</tr>
<tr>
<td>Age 3 to 14 years</td>
<td>1</td>
</tr>
<tr>
<td>Age 15 to 44 years</td>
<td>0</td>
</tr>
<tr>
<td>Age ≥ 45 years</td>
<td>-1</td>
</tr>
</tbody>
</table>

Modified Centor score: sensitivity 94% (95% CI 92-97%), specificity 54% (95% CI 49-59%). Lower specificity leans towards false positives & over-treatment.

Back-up throat cultures are recommended for negative lateral flow RADT in children.

- Diagnostic testing is not recommended if:
  - A modified Centor score of ≤1
  - Symptoms of a viral infection (rhinorrhea, cough, oral ulcers, hoarseness) **IDSA 2012 strong, high**
  - <3yrs, unless other risk factors e.g. sibling with GAS infection **IDSA 2012 strong, moderate**
  - Asymptomatic contact of patient with GAS pharyngitis **IDSA 2012 strong, moderate**

**Exceptions**: the modified Centor score may not accurately predict risk of GAS during epidemics or in high risk populations, e.g. individuals with a history of rheumatic fever, valvular heart disease, or immunosuppression. Use clinical judgment & consider testing (RADT/throat swab) more broadly.

**SHOULD ANTIBIOTICS BE USED TO TREAT PHARYNGITIS?**

- 80-90% of adults (>70% of children) do **NOT** require antibiotics as infection likely viral.
- Patients with a positive throat swab should receive an antibiotic to prevent complications. See modified Centor score on left column, & antibiotic table below.
- The turn-around-time for throat swab results can take a few days. However, antibiotics started within 9 days of symptom onset in confirmed GAS will prevent rheumatic fever.
- If antibiotics are started empirically, ensure agent is discontinued if throat swab negative.

**MOST COMMON BACTERIAL PATHOGEN**

- Group A Streptococcus (GAS) (outpatient Group C and G strep do not require antibiotics)

**EMPIRIC DRUG REGIMENS OF CHOICE & SUSCEPTIBILITY CONCERNS**

<table>
<thead>
<tr>
<th>FIRST LINE</th>
<th>- Majority of cases are viral.</th>
<th>- Only use antibiotics in confirmed bacterial pharyngitis.</th>
<th>- See Symptom Management following page.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No antibiotic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Penicillin V</strong></td>
<td>Peds: ≤27 kg: 40mg/kg/day ÷ BID or TID</td>
<td>&gt;27 kg &amp; Adults: 300mg TID x 10 days, or 600mg BID x 10 days</td>
<td>- <strong>1st line</strong> due to narrow spectrum of activity, efficacy, safety &amp; low cost.</td>
</tr>
<tr>
<td></td>
<td>Peds: ≤27 kg: 40mg/kg/day ÷ BID or TID x10 days (maximum 750mg/day)</td>
<td>Adults: 500mg BID x 10 days</td>
<td>- No documented resistance to GAS.</td>
</tr>
<tr>
<td><strong>Amoxicillin</strong></td>
<td>Peds: 40mg/kg/day ÷ BID or TID</td>
<td>Adults: 500mg BID x 10 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>x10 days (maximum 1000mg/day)</td>
<td></td>
<td>Compared to penicillin: - broader spectrum than required; as effective - liquid more palatable for children</td>
</tr>
<tr>
<td><strong>PENICILLIN ALLERGY: TYPE IV HYPERSENSITIVITY (e.g. rash)</strong></td>
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<tr>
<td><strong>Cephalexin</strong></td>
<td>Peds: 25-50mg/kg/day ÷ BID or QID</td>
<td>Adults: 250mg QID x 10 days, or 500mg BID x 10 days</td>
<td>- No documented resistance to GAS.</td>
</tr>
<tr>
<td></td>
<td>x10 days (maximum 1000mg/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PENICILLIN ALLERGY: TYPE I HYPERSENSITIVITY (i.e. anaphylaxis)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clindamycin</strong></td>
<td>Peds: 20mg/kg/day ÷ TID x10 days (maximum 900mg/day)</td>
<td>Adults: 300mg TID x 10 days</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td><strong>Clarithromycin</strong></td>
<td>Peds: 50mg/kg/day divided BID x10 days (maximum 500mg/day)</td>
<td>Adults: 250mg BID x 10 days</td>
<td></td>
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<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Erythromycin</strong></td>
<td>Peds: 40mg/kg/day ÷ BID or TID x10 days (maximum 2000mg/day)</td>
<td>Adults: 250mg QID x 10 days</td>
<td></td>
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<tr>
<td></td>
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<tr>
<td><strong>Azithromycin</strong></td>
<td>Peds: 12mg/kg/day daily x 5 days, or 20mg/kg/day daily x3 days (max 500mg/d)</td>
<td>Adults: 500mg Day 1, 250mg x Days 2-5, or 500mg daily x 3 days</td>
<td></td>
</tr>
</tbody>
</table>

**Macrolide considerations:**
- Clarithromycin x 10 days was superior to azithromycin x 5 days for bacterial eradication (NNT=9) in adults, but equivalent for clinical cure.
- ↑ GI side effects with erythromycin.
- Azithromycin 3 vs 5 days: no head-to-head trials. Both regimens provide same total dose over the course of therapy (i.e. 60mg/kg/d; 1.5g).
PHARYNGITIS: Management Considerations

**Duration of Antibiotic Therapy:**
- Confirmed bacterial pharyngitis should be treated with 10 days of antibiotics (exception: if azithromycin is used in penicillin allergic patients; other options available).
- Patients will likely have clinical improvement within the first few days of therapy, but 10 days of therapy is recommended for preventing acute rheumatic fever, & short courses are not as effective for treating the infection.
  - E.g. a meta-analysis comparing 5 vs 10 days of penicillin (2 RCTs, n=309) concluded short courses were inferior in achieving bacterial cure, OR 0.29 (CI 95% 0.13-0.63).

**SYMPTOM MANAGEMENT**

<table>
<thead>
<tr>
<th>SYSTEMIC ANALGESICS</th>
<th>SYMPTOM MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>e.g. Ibuprofen</td>
<td>- Ibuprofen ↓ associated pain more than acetaminophen &amp; placebo.</td>
</tr>
<tr>
<td>Adults: 400mg po q6-8hr PRN</td>
<td>- Reduces fever.</td>
</tr>
<tr>
<td>Peds: 5-10 mg/kg po q6-8hr PRN (maximum 40mg/kg/day)</td>
<td></td>
</tr>
</tbody>
</table>

**ACETAMINOPHEN**

- Less effective than NSAIDs for ↓ associated pain but more effective than placebo.
- Reduces fever.

**BENZOCaine**

- Alleviates throat pain if used frequently.
- Avoid in children due to:
  - risk of choking
  - concerns with methemoglobinemia

**PHENOL**

- No evidence, but anecdotally may provide relief from associated pain.

**Gargling or drinking warm liquids**

- e.g. warm salt water rinse, tea
- Benzydamine
  - gargle or rinse q1.5-3hr PRN

**Lozenges**

- TYLENOL, g
- BAFFLE, g
- Rinse 15mL

**Not recommended for symptom management:**

- Routine use of corticosteroids. ↓ in duration of pain is not considered clinically significant, and NSAIDs/acetaminophen have less adverse events.
- **Chinese herbal:** insufficient evidence to support use. If patient insists, encourage a product with a Natural Product Number (NPN).

**Treatment Evidence Summary**

**Penicillin vs Cephalosporins vs Macrolides:** penicillin remains the antibiotic of choice

- There is no clinically relevant difference in symptom resolution between the various antibiotics.
- Penicillin has the most evidence for preventing complications; has a narrow spectrum; is efficacious, safe, inexpensive; & there is no documented resistance to GAS.

**Clinical Q&A**

**What is the risk of acute rheumatic fever?**

- In Canada, the current prevalence of acute rheumatic fever is 0.1 to 2 cases per 100,000.
  - The incidence in some remote, Canadian Aboriginal communities may be higher (i.e. Northern Ontario 8.33/100,000).
  - The risk may also be higher in immigrants from endemic areas, e.g. Philippines, China.
- It is difficult to estimate the risk of acute rheumatic fever due to untreated pharyngitis:
  - as the majority of studies comparing antibiotics versus placebo were conducted prior to the 1960s (higher rate of acute rheumatic fever, and in young males from the US Armed Forces)
  - bacterial versus viral etiology was often not confirmed
  - newer studies have either no documented cases of acute rheumatic fever or did not assess this outcome
- In an effort to balance unnecessary antibiotic use with preventing rheumatic fever:
  - use the modified Centor score to identify patients who require a throat swab/RADT
  - avoid identifying asymptomatic carriers; may initiate antibiotics sooner
- A full 10 day course of penicillin is recommended for confirmed GAS pharyngitis.

**Pharyngitis caused by Chlamydia trachomatis**

- It is rare that Chlamydia trachomatis causes pharyngitis, but rates appear to be ↑.
- Risk factors include: age 15-24 years, sexually active, engagement in oral sex.
- In Saskatchewan, Chlamydia trachomatis screening requires a different lab requisition.
- Treatment: doxycycline 100mg po BID x 7days, or azithromycin 1g x 1 dose.

**Management of Recurrent Pharyngitis**

- Potential causes: recurrent pharyngitis due to inadequate eradication, new infection, viral infection in an asymptomatic carrier ~20% of the population are GAS carriers.
- Controversial as to whether or not asymptomatic carriers with recurrent pharyngitis need to be identified.
- Identification may help avoid antibiotics in those with recurrent viral pharyngitis.
- Avoid identifying asymptomatic carriers without recurrent pharyngitis.
- Also consider age, season, signs & symptoms to rule out a viral etiology (see modified Centor score).
- Avoid using continuous long-term antibiotic therapy (i.e. repeated courses or prophylaxis).

**Abbreviations:**

- GAS = Group A Streptococcus
- IDSA = Infectious Diseases Society of America
- NSAID = non-steroidal anti-inflammatory drug
- NNT = number needed to treat
- RADT = rapid antigen detecting test
PEAKS for the MANAGEMENT of ACUTE SINUSITIS

- Most cases do NOT require antibiotics as 98-99.5% of infections are viral.
- Viral & bacterial sinusitis have similar symptoms, but symptoms that worsen or are prolonged (≥10 days) suggest bacterial involvement.
- Advise on treatments that provide symptomatic relief: analgesics, saline nasal drops/rinses, decongestants, warm facial packs, & corticosteroids.
- Amoxicillin is the antibiotic of choice for bacterial sinusitis. Reserve macrolides for patients with true penicillin allergies.
- Patients should see their healthcare provider if symptoms worsen or take longer than 10 days to resolve.

PRE-TREATMENT CONSIDERATIONS

- Inappropriate antibiotic use is driving resistance & leading to a crisis. Please examine your own prescribing practices. Refer to newsletter cover.

ACUTE SINUSITIS

- Viral Sinusitis: antibiotics NOT required
- Bacterial Sinusitis: antibiotics NOT required
- Bacterial Sinusitis: may require antibiotics

- Prediction rules have been developed to help distinguish bacterial from viral sinusitis. However, due to limitations with these, the guidelines instead focus on the presence & duration of the above 3 symptoms. Acute viral sinusitis symptoms tend to improve within 1wk.
- The colour of mucus should not be used to diagnosis a bacterial sinusitis infection (indicative of inflammation, but not of bacteria).
- Sinusitis is self-limiting. ~85% of bacterial cases will improve within 2 weeks without antibiotics. In other words, out of 1000 patients presenting with sinusitis, 5 to 20 patients would have bacterial sinusitis, and 4 to 17 of these bacterial cases would resolve without antibiotics.
- Compared to placebo, antibiotics (beta-lactams, macrolides, FQ) have not been shown to ↓duration of pain or illness. The NNT for clinical improvement is high (NNT=7 to 18), & a systematic review including patients with symptoms for ≥7 days failed to show a benefit with antibiotics. Antibiotic AE primarily GI related were common (NNH=8 to 12).

SYMPTOM MANAGEMENT

- Acetaminophen
  - 10-15mg/kg q4-6hr PRN (max 75mg/kg/day)
  - 1000mg po q6hr PRN (max 3.2-4g/day)
- Ibuprofen
  - 5-10mg/kg q6-8hr (max 40mg/kg/day)
- 400mg po q6-8hr PRN
- Xylometazoline (≥12 yrs & adults): 2-3 sprays/nostril q8-10hr PRN
- Pseudoephedrine: 6-11yrs: 30mg po q4-6hr PRN, or 120mg ER po q12h PRN
  - Limitation: may provide benefit for severe sinusitis, in combination with an antibiotic (NNT=7 for symptom improvement or resolution). No benefit with monotherapy.
- Prolonged symptoms, pain & nasal congestion (NNT=15/2-3wks), vs placebo. May lessen symptoms by 3.5 vs placebo. May lessen symptoms by 3.5
- ORAL:
  - Fluticasone
    - 50 mcg 2 sprays in each nostril once daily
  - Mometasone
    - 3 sprays/nostril twice daily
  - Oral: nasaldex (not recommended in <3yrs)
  - Prednisone 40 to 60mg po daily x 7 days
- INTRANASAL: modestly effective for pain & nasal congestion (NNT=15/2-3wks), vs placebo. May lessen symptoms by 3.5 days. Mild AE (e.g. epistaxis, nasal itching).
- INTRANASAL: may relieve congestion & promote sinus drainage.
- Topical preparations: less systemic absorption (oral AE: CV, insomnia); limit to 3-5 days to prevent rebound symptoms
- INTRANASAL:
  - OTRIVIN
    - May relieve congestion & promote sinus drainage.
  - NASONEX
    - Fluticasone
      - 50 mcg 2 sprays in each nostril once daily
    - Mometasone
      - 50 mcg 2 to 4 sprays each nostril twice daily
  - Fluticasone (≥12 yrs & adults): 60mg po q8-10hr PRN, or 120mg ER po q12h PRN
- SUDAFED
  - Topical preparations: less systemic absorption (oral AE: CV, insomnia); limit to 3-5 days to prevent rebound symptoms
  - Pseudoephedrine
    - 6-11yrs: 30mg po q4-6hr PRN (max 120mg/d)
    - ≥12 yrs & adults: 60mg po q4-6hr PRN, or 120mg ER po q12h PRN

CORTICOSTEROIDS

- Prednisone 40 to 60mg po daily x 7 days
- No quality evidence but should reduce fever & treat localized pain.
- No quality evidence but anecdotally may promote mucus drainage.
- Anecdotally, nasal drops/sprays may help.
- Limited conflicting evidence with nasal irrigation; may ↑mucociliary clearance & ↑quality of life, ↑microbial clearance & ↓use of other sinusitis medications.

ACUTE SINUSITIS

- Viral sinusitis: antibiotics NOT required
- Bacterial sinusitis: antibiotics NOT required
- Bacterial sinusitis: may require antibiotics

- Prediction rules have been developed to help distinguish bacterial from viral sinusitis. However, due to limitations with these, the guidelines instead focus on the presence & duration of the above 3 symptoms. Acute viral sinusitis symptoms tend to improve within 1wk.
- The colour of mucus should not be used to diagnosis a bacterial sinusitis infection (indicative of inflammation, but not of bacteria).
- Sinusitis is self-limiting. ~85% of bacterial cases will improve within 2 weeks without antibiotics. In other words, out of 1000 patients presenting with sinusitis, 5 to 20 patients would have bacterial sinusitis, and 4 to 17 of these bacterial cases would resolve without antibiotics.
- Compared to placebo, antibiotics (beta-lactams, macrolides, FQ) have not been shown to ↓duration of pain or illness. The NNT for clinical improvement is high (NNT=7 to 18), & a systematic review including patients with symptoms for ≥7 days failed to show a benefit with antibiotics. Antibiotic AE primarily GI related were common (NNH=8 to 12).

PRE-TREATMENT CONSIDERATIONS

- Sinusitis complications are very rare, e.g. orbital, intracranial or soft tissue infections. See alarm symptoms on next page. Incidence is similar among those treated with antibiotics versus placebo (<0.1%).
- Sinusitis is very rare in children (<9 years) due to underdeveloped sinus cavities.

### Most Common Bacterial Pathogens
- *S. pneumoniae, H. influenzae, M. catarrhalis* (in children), *S. aureus*

### Empiric Drug Regimens of Choice

#### Mild to Moderate (Symptoms <10 days or no worsening in symptoms)

**No Antibiotic**
- 98-99.5% of cases are viral
- See symptom management

#### Mild to Moderate (Symptoms ≥10 days or worsens within 10 days)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Empirical Drug Regimens of Choice</th>
<th>Comment</th>
</tr>
</thead>
</table>
| **Amoxicillin**  | Peds: 40-90mg/kg/day ÷ BID or TID x 10 days (maximum 3g/day)  
                   Adults: 500mg to 1000mg po TID x 5 - 10 days*  
                   - *S. pneumoniae* susceptible to high-dose amoxicillin, even isolates with intermediate susceptibility.  
                   - Covers all of the common bacterial pathogens.  
                   - Addition of clavulanate ↑ risk of GI AE (use 7:1 ratio formulation & BID dosing to lessen).  
| **Amoxicillin / Clavulanate**  
                   CLAVULIN 4:1 or 7:1 ratio  
                   Dose listed as per amox component | Peds: 45mg/kg/day (±45mg/kg/day amoxicillin ÷ BID) (max total daily dose of amox is 3g)  
                                           Adults: 500mg po TID (or 875mg po BID of 7:1 ratio form) x 5 - 10 days*  
| **Penicillin Allergy: Type IV Hypersensitivity (e.g. rash)** | Cefuroxime  
                   Peds: 30-40mg/kg/day ÷ BID (max 1000mg/day) x 10 days  
                                           Adults: 250mg to 500mg po BID x 5 - 10 days*  
| **Penicillin Allergy: Type I Hypersensitivity (i.e. anaphylaxis)** | Doxycycline  
                   Peds: ≥ 9 years: 4mg/kg/day ÷ BID (max 200mg/day) x 10 days  
                                           Adults: 200mg po Day 1, then 100mg po BID x 5 - 10 days*  
                   Clarithromycin*  
                   Peds: 15mg/kg/day ÷ BID (max 500mg/dose) x 5-10 days  
                                           Adults: 500mg po BID or 1000mg XL po daily x 5 - 10 days*  
| **Azithromycin¶**  
                   Peds: 10mg/kg Day 1, then 5mg/kg daily Days 2-5  
                                           (maximum 500mg Day 1, 250mg Days 2-5)  
                                           Adults: 500mg po Day 1, then 250mg po daily Days 2-5  
| **Ceftazidime**  
                   Peds: 40-120mg/kg/day ÷ BID or TID x 10 days (maximum 3g/day)  
                   Adults: 500mg to 1000mg po TID x 5 - 10 days*  
                   - *S. pneumoniae* susceptible to high-dose amoxicillin, even isolates with intermediate susceptibility.  
                   - Covers all of the common bacterial pathogens.  
                   - Addition of clavulanate ↑ risk of GI AE (use 7:1 ratio formulation & BID dosing to lessen).  
| **PENICILLIN ALLERGY: TYPE IV HYPERSENSITIVITY (e.g. rash)** | Cefuroxime  
                   Peds: 30-40mg/kg/day ÷ BID (max 1000mg/day) x 10 days  
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                                           Adults: 200mg po Day 1, then 100mg po BID x 5 - 10 days*  
                   Clarithromycin*  
                   Peds: 15mg/kg/day ÷ BID (max 500mg/dose) x 5-10 days  
                                           Adults: 500mg po BID or 1000mg XL po daily x 5 - 10 days*  
| **Azithromycin¶**  
                   Peds: 10mg/kg Day 1, then 5mg/kg daily Days 2-5  
                                           (maximum 500mg Day 1, 250mg Days 2-5)  
                                           Adults: 500mg po Day 1, then 250mg po daily Days 2-5  

*5 days of therapy should be sufficient in uncomplicated adults. See below.  
*Clarithromycin is the preferred macrolide, unless major drug interactions (e.g. warfarin, digoxin, statin), as azithromycin may lead to more resistance (re: 1%).

### Treatment Evidence Summary

#### Duration of Therapy, if Needing to Treat with an Antibiotic
- In healthy adults suffering from sinusitis, short courses (e.g. 5 days) have the same benefit as longer courses of therapy (e.g. 10 days), with less harm.
- A meta-analysis (12 RCTs, n=4430) found no difference in clinical success (cure or improvement of symptoms) with short courses (3 to 7 days) versus longer courses (6 to 10 days) of the same antibiotic. A sensitivity analysis (7 RCTs, n=2715) comparing 5 versus 10 days did not find a difference in clinical success either. Overall, there was no difference in adverse events. However, in the sensitivity analysis (5 vs 10 days), short courses had fewer adverse events (OR 0.79, 95% CI 0.63-0.98).
- Older patients with comorbidities were excluded from the trials, and therefore we do not have evidence to support a shorter course of therapy in this population.
- A longer course of therapy (i.e. 10 days) is still recommended for children, based on the available evidence.

### When should patients with sinusitis be referred to a specialist?
- **Recurrent Sinusitis:** ≥4 episodes of acute bacterial sinusitis/year  
  - Neither antibiotics nor intranasal steroids have shown a reduction in the recurrent sinusitis episodes.  
  - Consider assessment for allergies, immunologic deficiency, or surgery.
- **Chronic Sinusitis:** ≥12 weeks of inflammation plus ≥2 of the following: mucopurulent discharge, nasal congestion, facial pain-pressure-fullness, or ↓ sense of smell.  
  - Consider intranasal corticosteroids ± saline irrigation for symptom management.  
  - Repeated courses of antibiotics are not recommended.  
  - Consider referral to an Ears/Nose/Throat specialist if above measures fail.

### Alarm Symptoms for Urgent Referral to Emergency Room
- Systemic toxicity; altered mental status; severe headache; swelling of the orbit or change in visual acuity; black, necrotic tissue or discharge

### Antibiotic Treatment Evidence Summary

#### Amoxicillin vs Amoxicillin/Clavulanate:
- Amoxicillin is considered the antibiotic of choice due to its efficacy, safety, low cost, narrow spectrum, & quantity of evidence (most studied antibiotic for this indication).
- Amoxicillin covers *S. pneumoniae*. Effectiveness of high-dose amoxicillin (1000mg po TID, or 90mg/kg/day in children) extends to isolates with intermediate susceptibility.
- Amoxicillin-clavulanate provides broader coverage, specifically towards beta-lactamase producing bacteria (e.g. *H. influenzae, M. catarrhalis*). However, the addition of clavulanate ↑ the risk of GI adverse events. The higher amoxicillin to clavulanate ratio with the BID dosing (7:1) ↓ the risk of moderate/severe diarrhea vs TID (4:1) (BID 3.4% vs TID 5.9%, NNH=40), & may be more convenient.
- Either high-dose amoxicillin or amoxicillin-clavulanate may be preferred in the following patients:
  - Antibiotic use in the past month  
  - Age >65 years  
  - Severe sinusitis infection (e.g. systemic toxicity with temperature ≥39°C)  
  - Recent hospitalization  
  - Immunocompromised
- Amoxicillin-clavulanate may be preferred in the following patients:
  - Healthcare providers  
  - Close contact with child in daycare or treated individuals  
  - Protracted symptoms or history of sinusitis  
  - Treatment failure with amoxicillin  
  - Comorbidities (e.g. diabetes or chronic cardiac, hepatic or renal disease)  
  - Smoker or exposed to second-hand smoke in the same household
- **Doxycycline** also covers all of the potential bacterial pathogens.

### Clinical Q&A

*AE=adverse events  CV=cardiovascular  ER=extended release  FQ=fluoroquinolones  GI=gastrointestinal  NNH=number needed to harm  NNT=number needed to treat  RCT=randomized controlled trial*
Oral Antibiotics: Overview

- **Time vs Concentration Dependent Killing**: In time-dependent killing, an antimicrobial will be effective at any concentration above the MIC. A general rule of thumb is that serum levels should be above the MIC for >50% of the dosing interval. In concentration-dependent killing, an antimicrobial is more effective at a higher dose. Thus achieving a high peak (e.g., >10x) relative to the MIC is ideal.

- **Bacteriostatic vs Bactericidal**: Bacteriostatic agents inhibit the further growth of bacteria. Bactericidal agents actively destroy existing bacteria. Classifications are not absolute - for example, agents may be bacteriostatic in most situations but bactericidal at high concentrations, or bacteriostatic against some organisms and bactericidal against others.

- **Gram staining**: Gram-positive bacteria appear purple under a Gram stain, due to retention of crystal violet dye in their thick peptidoglycan cell walls. Gram-negative bacteria appear red and have thinner cell walls.

- **Enterobacteriaceae bacteria**: e.g., *Citrobacter, E. coli, Enterobacter, Klebsiella, Morganella, Proteus, Salmonella, Serratia, Shigella*. Group of Gram-negative bacilli often found in the GI tract.

- **Anaerobic bacteria**: e.g., *Peptococcus, Peptostreptococcus, B. fragilis, Prevotella*. By definition, do not require oxygen to survive. Found as normal flora in the mouth and GI tract. Anaerobic coverage can be important in situations such as aspiration pneumonia, intra-abdominal infections, and diabetic foot ulcers. Antimicrobials with good activity include metronidazole, clindamycin, amox-clav, and moxifloxacin.

- **Atypical bacteria**: e.g., *Mycoplasma, Chlamydia, Legionella*. These bacteria lack a cell wall. As a result, they cannot be viewed under a gram stain and are naturally resistant to all beta-lactams. Antimicrobials with good activity include macrolides, fluoroquinolones, and tetracyclines.

- **Beta-Lactamase**: Important mechanism bacteria use to resist penicillins. Beta-lactamase is an enzyme which cleaves the beta-lactam ring. Common beta-lactamase producers include *Haemophilus influenzae, Neisseria gonorrhoeae, Moraxella catarrhalis, Escherichia coli, Proteus, Klebsiella*, and *Bacteroides fragilis*. Adding clavulanic acid to amoxicillin can renew coverage to these organisms. Unfortunately, resistance can still occur — such as through Extended-Spectrum Beta-Lactamase (ESBL) (esp. in *E. coli, Proteus, and Klebsiella*). Organisms producing ESBL tend to be resistant to all penicillins, all cephalosporins, usually all beta-lactam/beta-lactamase inhibitor combinations ... and may show multi-drug resistance to other classes (e.g., aminoglycosides, fluoroquinolones, tetracyclines). In the Regina Qu’Appelle Health Region in 2014, 3.5% of *E. coli* and 0.89% of *Klebsiella pneumoniae* isolates were ESBL positive.

- **MSSA & MRSA**: *Staph aureus* was originally susceptible to all penicillins. However, today *Staph aureus* is reliably resistant to penicillin, amoxicillin, and ampicillin through beta-lactamase production. In response, beta-lactamase-resistant antibiotics were invented, like methicillin, cloxacillin, and oxacillin. Further, beta-lactamase inhibitors like clavulanic acid were invented. Cloxacinil and amox-clav are able to kill methicillin-sensitive *Staph aureus* (MSSA). Unfortunately, *Staph aureus* resistant to methicillin (i.e., MRSA) soon emerged. MRSA is resistant to all beta-lactams; alternative agents must be used. Community-Associated MRSA (CA-MRSA) is defined as MRSA in patients who have not been hospitalized in the previous 12 months. CA-MRSA is less likely to be multi-drug resistant.

- **High-risk AECOPD**: presence ≥ 1 of the following → severe COPD or worse (i.e. FEV1 < 50%); ≥ 4 exacerbations per year; ischemic heart disease; use of home O2; chronic oral corticosteroids; antibiotic use in the past 3 months.

- **Complicated UTIs**: lacks standard definition, but resistant organisms appear more likely if 1 or more of the following risk factors → signs and symptoms for greater than 7 days; male sex; renal failure; immunosuppression; diabetes (especially if long-term complications i.e. neuropathy); catheterization; structural abnormality; obstruction; recent urogenital procedure; spinal cord injury.

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### Quick References

#### Antibiotics During Pregnancy/Lactation

<table>
<thead>
<tr>
<th>Antibiotics During Pregnancy/Lactation</th>
<th>Safe / Likely Safe / Caution / Contraindicated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FLUOROQUINOLONES</strong></td>
<td></td>
</tr>
<tr>
<td>Erythromycin – non-estolate</td>
<td>1st Trimester: risk of maternal hepatotoxicity</td>
</tr>
<tr>
<td>Erythromycin estolate ILOSONE</td>
<td>2nd Trimester: safer alternatives usually available</td>
</tr>
<tr>
<td>Azithromycin / Clarithromycin</td>
<td>3rd Trimester: normal uterine contraction</td>
</tr>
<tr>
<td>Amoxicillin + clav / Ampicillin</td>
<td>Lactation: tetracycline</td>
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<tr>
<td>Claxacinil / Penicillin V</td>
<td></td>
</tr>
<tr>
<td><strong>CEPHALOSPORINS</strong></td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>abnormal teeth &amp; bone development, malformations, maternal hepatotoxicity</td>
</tr>
<tr>
<td>Cotrimoxazole SEPTRA, BACTRIM</td>
<td>doxy-, mino-cycline</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>hemolytic anemia, neonate jaundice, kernicterus</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>ok in healthy term infants without G6PD deficiency</td>
</tr>
<tr>
<td>Metronidazole (oral)</td>
<td>1st trimester: accumulated data suggests likely safe</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>may hold breastfeeding 12-24hr post tx</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>avoid in infants &lt; 4 mos &amp; G6PD deficiency</td>
</tr>
</tbody>
</table>

**Note:**

- **MACRO**: monotherapy with macrolides, fluoroquinolones, and tetracyclines.
- **NOS**: Risk of maternal hepatotoxicity.
- **CNS**: Risk of CNS depression (RR 1.4).
- **HBP**: Hypertension (RR 2.0).
- **G6PD**: Glucose-6-phosphate dehydrogenase.
- **GDP**: Glucose-6-phosphate.
- **PK**: Pharmacokinetics.
- **PK**: Pharmacodynamic.
- **LD**: Limitation of duration of therapy.
- **HIV**: Human immunodeficiency virus.
- **G6PD**: Glucose-6-phosphate dehydrogenase.
- **SJS**: Stevens Johnson syndrome.
- **VRE**: Vancomycin resistant enterococcus.
- **PJP**: Pneumocystis jiroveci.
- **RVT**: Respiratory tract infection.
- **UTI**: Urinary tract infection.
- **PH**: Pneumonia.
- **FEP**: Fluoroquinolone.

---

#### Cephalosporin Generations

<table>
<thead>
<tr>
<th>Cephalosporin Generations</th>
<th>(available in Canada)</th>
</tr>
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<tbody>
<tr>
<td>1st</td>
<td>cephalexin (po)</td>
</tr>
<tr>
<td>2nd</td>
<td>cefuroxime (po/IV/IM)</td>
</tr>
<tr>
<td>3rd</td>
<td>cefaclor (po)</td>
</tr>
<tr>
<td>4th</td>
<td>cefoxitin (IV/IM)</td>
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</table>

**Note:**

- In anaphylactic penicillin allergies, the risk of cross-reactivity with cephalosporins is low (1-2%); however, the usual recommendation is to avoid cephalosporins. (Some suggest that risk increases with similar side-chains - i.e. amoxicillin or ampicillin with ceprozil or cephalaxin; penicillin with cefozolin.)

- In patients who have only had a penicillin rash, the risk of reaction is <0.1%. The usual recommendation is that cephalosporins are safe. Consider referral to an Allergy specialist.

Which antimicrobials are most associated with *Clostridium difficile* colitis?

- Risk of *C. difficile* is essentially zero without antibiotic exposure. Most antibiotics carry some risk. Greatest risk appears to be with clindamycin (OR 16.8 vs no antibiotic exposure), cephalosporins, and fluoroquinolones.17

Which antimicrobials are most associated with QT prolongation?

- For patients at risk of QT-prolongation, effect appears greatest with macrolides (clarithro, erythro > azithro) & fluoroquinolones (especially moxifloxacin and levofloxacin).
Dosing Amoxicillin

125, 250mg chew tab cherry 25, 50mg/mL susp strawberry, banana, sugar free, berry 250, 500mg cap 1st trimester: ??left lip/palate. Amoxicillin risk 2-4/1000 vs baseline risk of 1-2/1000

Coverage: Streptococci; Enterococcus faecalis; Listeria; N. meningitidis.

Useful in: upper respiratory tract infections; sinusitis; acute otitis media; dental procedure prophylaxis; low-risk AECOPD. Strup pneumo resistance only 3% in Canada for community-treated infections.

High pediatric doses (e.g. 90mg/kg/day) can overcome moderate Strup pneumo resistance in acute otitis media & community acquired pneumonia. Risk factors for PRSP: recent antibiotic use, daycare, not given PREVAR.

Consider watchful waiting in acute otitis media for suitable children (see page 78).

Excellent bioavailability. Achieves high concentrations in the middle ear.

Amoxicillin AMOXIL, g

- Strength listed is component amoxicillin. Clavulanate component is 125mg.
- Coverage as per amoxicillin, plus: MSSA, many Enterobacteriaceae; Haemophilus influenzae; Moraxella; many anaerobes.
- Max dose: 2000-4000mg/day
- Useful in: bite wounds; respiratory tract infections; high-risk AECOPD
- ↑ diarrhea vs amoxicillin NNI=10. Less diarrhea with q12h dosing vs q8h.
- Coverage: Streptococci; Enterococcus faecalis; Listeria; N. meningitidis. [Same spectrum as amoxicillin.]
- Useful in: UTIs with sensitive enterococci; meningitis (IV formulation, as part of combo therapy).
- Disadvantages vs amoxicillin: ↑ absorption, ↓ convenience (q8h), & ↑ AE (diarrhea, due to incomplete absorption). Good CSF penetration. Useful in severe listeria infections due to availability of an IV formulation.

Ampicillin, g

250, 500mg cap 1st trimester: see amoxicillin

Coverage: MSSA by definition; some Streptococci (penicillin covers more Streptococci species).

Useful in: Skin and soft tissue infections (where primarily MSSA). Narrow-spectrum agent; often used as step-down therapy when MSSA is known pathogen.

Methicillin, oxacillin, & dicloxacillin options in countries outside of Canada and have equivalent spectrum.

Cloxacillin, g

25mg/mL susp cherry 250, 500mg cap 60mg/mL sol'n fruity 300mg (480,000 unit) tab

Coverage: Streptococci; oral anaerobes (e.g. Actinomyces, Clostridium perfringens, Peptostreptococci, Propionibacterium). Still no resistance with Group A Streptococcus (aka Streptococcus pyogenes).

Useful in: bacterial pharyngitis; rheumatic fever prophylaxis (prophylactic dose is 250mg po q12h)

q12h dosing in pharyngitis appears effective.

Penicillin V Potassium PEN-VK, g

25mg/mL sol'n fruity 50-100mg/kg/day divided q6h

60mg/mL sol'n fruity 25-50mg/kg/day divided q6-12h

300mg (480,000 unit) tab 15-30mg/kg/day divided q12h

Cephalosporins


All cephalosporins lack coverage of Listeria, atypicals, MRSA, & Enterococci (LAME). Gonorrea resistance to cefixime ~ 2% in Canada (combine cefixime with a macrolide due to resistance + add clamidya coverage).4 5

AE: rash, nausea, diarrhea. Rare: allergic reactions, cytopenias.

DI: can ↑INR with warfarin; May cause oral contraceptive failure. X signs of anaphylaxis. True penicillin anaphylactic allergy: 0.01% of population. PK: Amoxicillin and amox/clav have excellent bioavailability.

Cephalexin KEFLEX, g

25, 50mg/mL orange-banana 25, 500mg tab

Coverage: Streptococci; MSSA; ?Proteus; E. coli; Klebsiella. (PEK)

Useful in: skin and soft tissue infections; step down option from IV cefazolin.

Take with food to reduce GI upset.

Cefadroxil DURICEF, g 500mg cap ↑▼ 250mg tab

1st-generation cephalosporins.

Coverage: Streptococci; MSSA; ?Proteus; E. coli; Klebsiella. (PEK)

Useful in: skin and soft tissue infections; step down option from IV cefazolin.

Cefprozil CEFZIL, g 25, 50mg/mL susp bubblegum 250, 500mg tab

2nd-generation cephalosporins.

Coverage: Streptococci; MSSA; Moraxella; Haemophilus influenzae; Proteus; E. coli; Klebsiella. (H PEK)


Cefuroxime axetil CEFTIN, g 25mg/mL susp 250mg sachet tutti-frutti 250, 500mg tab

3rd-generation cephalosporins. Coverage: Streptococci; Moraxella; Haemophilus influenzae; ?Enterobacter; Neisseria; Proteus; E. coli; Klebsiella; Serratia. (HEN PECKS)

Useful in: gonorrea (800mg po x1 dose + azitro); pyelonephritis or complicated UTIs; low-risk AECOPD.

Cefixime SUPRAX, g 20mg/mL susp strawberry 400mg tab

3rd-generation cephalosporin. Coverage: Streptococci; Moraxella; Haemophilus influenzae; ?Enterobacter; Neisseria; Proteus; E. coli; Klebsiella; Serratia. (HEN PECKS)

Used in hospitalized pts for empiric coverage of gram-negative infections; also useful in an out-patient setting (e.g. one-time IM dose for gonorrea; initial treatment of suspected pyelonephritis while waiting for cultures).

Ceftriaxone Injection ROCEPHIN, g 1, 2, 10g vials for injection (IM/IV) X

3rd-generation cephalosporin with excellent gram-negative coverage (e.g. Citrobacter, E. coli, Klebsiella, Morganella, Proteus, Serratia).

Used in hospitalized pts for empiric coverage of gram-negative infections; also useful in an out-patient setting (e.g. one-time IM dose for gonorrea; initial treatment of suspected pyelonephritis while waiting for cultures).

Cefuroxime axetil CEFTIN, g

- Coverage: Streptococci; Moraxella; Haemophilus influenzae; Proteus; E. coli; Klebsiella. (H PEK)
- Cefuroxime has poor bioavailability (37% fasting; 52% with food). Cefprozil has excellent bioavailability.

Cefuroxime axetil CEFTIN, g 25mg/mL susp 250mg sachet tutti-frutti 250, 500mg tab

- Coverage: Streptococci; Moraxella; Haemophilus influenzae; Proteus; E. coli; Klebsiella. (H PEK)
- Cefuroxime has poor bioavailability (37% fasting; 52% with food). Cefprozil has excellent bioavailability.

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- Cefuroxime has poor bioavailability (37% fasting; 52% with food). Cefprozil has excellent bioavailability.
### Oral Antibiotics (continued)

**Dosing** with adequate dose & appropriate duration

<table>
<thead>
<tr>
<th>Generic/Trade</th>
<th>Adverse Events AE</th>
<th>Contraindications CI</th>
<th>Drug Interactions DI</th>
<th>Monitor M</th>
<th>Comments</th>
<th>Dosing (Adult, Pediatric, Usually Max)</th>
<th>Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macrolides</strong></td>
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<tr>
<td>- <strong>Azithromycin</strong> (ZITHROMAX, g)</td>
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<td>20, 40mg/mL susp cherry</td>
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<td>250mg tab</td>
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<td>600mg tab</td>
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<tr>
<td>After reconstitution, suspension may be kept at room temperature.</td>
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</tbody>
</table>
| - Coverage: *Streptococci; N. gonorrhoeae; Moraxella; Haemophilus influenzae; Legionella;* many atypicals.
| - Useful in: pneumonia; upper respiratory tract infections; low-risk AECOPD; MAC prophylaxis in HIV pts; but Dls with HIV medications possible.
| - Keep reconstituted suspension at room temperature.
| - XL tab = with food & once daily. Regular tab = with or without food. | | | | | | | |
| - Azithromycin appears more likely to lead to resistance than clarithromycin, as its long-half life results in prolonged sub-inhibitory levels at the end of therapy. | | | | | | | |
| - ? CV risk $\rightarrow$ some retrospective cohort studies have found increased risk of cardiovascular mortality compared to amoxicillin (estimated 47 additional deaths per 1 million courses), although other studies have found no risk. 16-19
| - Has additional anti-inflammatory activity (occasionally used chronically in COPD, cystic fibrosis, etc. to $\downarrow$ pulmonary inflammation – but efficacy is limited). | | | | | | | |
| **Clarithromycin** (BIAXIN, g) | | | | | | | |
| 25, 50mg/mL susp fruity | | | | | | | |
| 250, 500mg tab | | | | | | | |
| 500mg XL tab | | | | | | | |
| - Coverage: *Streptococci; Moraxella; Haemophilus influenzae; Legionella;* many atypicals. (Unlike other macrolides, lacks H. influenzae coverage - therefore not recommended as empiric therapy for pneumonia in adults or in AECOPD. Reasonable option for pneumonia in kids < 12 years as *H. influenzae* uncommon in this group.)
| - Useful in: upper respiratory tract infections; acne; pneumonia if sensitive pathogen is cultured; pregnancy (non-estolate formulation).
| - Has been used to increase GI motility e.g. in gastroparesis, but resistance concerns development of tachyphylaxis with long-term use limit this indication. 34
| - Estolate formulation: contraindicated in pregnancy (↑ hepatotoxicity), but best in kids as most acid stable.
| - Empty stomach ideal for increased absorption, but if not tolerated, taking with food decreases GI upset.
| - Erythromycin unsafe in porphyria. | | | | | | | |
| **Erythromycin, g** | | | | | | | |
| ERYC 250, 333mg cap | | | | | | | |
| Erythromycin base 250mg tab | | | | | | | |
| Erythromycin Stearate 250mg tab (500mg x ▼) | | | | | | | |
| Erythromycin Estolate 50mg/mL susp ⇑ | | | | | | | |
| - Non-estolate: | | | | | | | |
| - Estolate: | | | | | | | |
| - Coverage: *Streptococci; Moraxella; Legionella;* many atypicals. (Unlike other macrolides, lacks H. influenzae coverage - therefore not recommended as empiric therapy for pneumonia in adults or in AECOPD. Reasonable option for pneumonia in kids < 12 years as *H. influenzae* uncommon in this group.)
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| - Estolate formulation: contraindicated in pregnancy (↑ hepatotoxicity), but best in kids as most acid stable.
| - Empty stomach ideal for increased absorption, but if not tolerated, taking with food decreases GI upset.
| - Erythromycin unsafe in porphyria. | | | | | | | |
| **Tetracyclines** | | | | | | | |
| - **Doxycline** (DOX, DOXYCIN, g) 100mg cap, tab | | | | | | | |
| - Coverage: Broad spectrum agent $\rightarrow$ *Staphylococci* (& often MRSA); *Strep pneumoniae*; *Moraxella; Haemophilus influenzae*; many atypicals; many anaerobes including spirochetes.
| - Useful in: pneumonia; low-risk AECOPD, purulent skin & soft tissue infections; rickettsia; acne; Lyme disease
| - Better absorption on empty stomach (↑20%), but may take with food to improve tolerability if necessary.
| - Dosing at 100mg once daily OK in acne & malaria prophylaxis. | | | | | | | |
| **Minocycline** (MIN, MINOCIN, g) 50, 100mg cap | | | | | | | |
| - Coverage: Broad spectrum agent $\rightarrow$ *Staphylococci; Strep pneumoniae; Moraxella; Haemophilus influenzae*; many atypicals; many anaerobes including spirochetes.
| - Useful in: some prosthetic joint infections; acne.
| - Due to association with serious rare AE, some suggest avoiding minocycline (doxycycline safer and effective). | | | | | | | |
| **Tetracycline** (TET, TETRACYN, g) 250mg cap | | | | | | | |
| - Coverage: Broad spectrum agents $\rightarrow$ *Staphylococci; Strep pneumoniae; Moraxella; Haemophilus influenzae*; many atypicals; many anaerobes including spirochetes.
| - Useful in: acne; actinomycosis; periodontitis.
| - Take TET on empty stomach - absorption is $\downarrow$ by food & dairy. | | | | | | | |

**Discontinued Products:** Erythromycin/Sulfisoxazole PEDIAZOLE suspension; Erythromycin Ethylsuccinate ERYPED suspension; Telithromycin KETEK tablet.

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*Pg 12*
### Oral Antibiotics (continued)

<table>
<thead>
<tr>
<th><strong>Generic</strong></th>
<th><strong>Trade</strong></th>
<th><strong>AE</strong></th>
<th><strong>CI</strong></th>
<th><strong>Drug Interactions</strong></th>
<th><strong>Monitor</strong></th>
<th><strong>Comments</strong></th>
<th><strong>Dosing (Adult, Pediatric, Usual Max)</strong></th>
<th><strong>$/10d</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fluoroquinolones</strong></td>
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<tr>
<td>• Inhibits DNA-gyrase, causing breakdown of bacterial DNA. Bactericidal. Concentration dependent killing (aim for high peak concentrations).</td>
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<tr>
<td>• <strong>AE</strong>: GI upset; rash/photosensitivity; ↑ QT; confusion/psychosis; ↑ or ↓ BG; seizure; tendinopathy/tendon rupture; retinal detachment; ↑ weakness in myasthenia gravis; articular damage in kids; hepatotoxicity; nephrotoxicity.</td>
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<tr>
<td>• <strong>DI</strong>: CYP1A2 inhibition → ↑ levels of clozapine, duloxetine, methotrerase, quinapril, rasagline, ropinirole, theophylline, tizanidine, varenicline, ↓ INR with warfarin. QT prolongation (watch for other QT-prolonging agents).</td>
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<tr>
<td>• ↓ absorption via chelation with Ca++, Fe++, AI++, Mg++ (may space calcium, iron, multivitamins, etc. by giving 2+ hours after fluoroquinolone, or hold for duration of fluoroquinolone therapy). Binds to enteral tubules (due to cations in feed - calcium, iron, etc.). May have less absorption via jejunostomy tube since fluoroquinolones are likely absorbed in the duodenum. Increased absorption may occur with corticosteroids.</td>
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<tr>
<td>• <strong>CI</strong>: See adverse effects. Safety &lt; 18 years not proven (but ciprofloxin in particular often used). If prolonged therapy: CBC, SCR, LFTs. ↑ ciprofloxacin, levofloxacin, moxifloxacin = excellent bioavailability.</td>
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<tr>
<td>• <strong>Reserve fluoroquinolones whenever possible.</strong></td>
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</table>

#### Why?
- These are broad-spectrum agents, with particularly good coverage against gram-negative pathogens. Preventing resistance, by limiting fluoroquinolone use, is important.
- Ciprofloxin has reliable anti-pseudomonal activity; agents that kill *Pseudomonas* are uncommon. Note: *Pseudomonas* suspected in serious infection, may use combination therapy empirically.

#### When might use be necessary?
- Patients with contraindications to other therapies (e.g. true penicillin allergies).
- Patients with infections resistant or likely to be resistant to other therapies.

---

### Fluoroquinolone use discouraged in < 18 yrs.

- Ciprofloxin (CIPRO, g)
  - **250, 500, 750mg tab**
  - **500mg XL tab**
  - **100mg/mL susp**
  - **NIHB** x 30 days maximum
  - **Coverage**: Primarily gram-negative coverage → *Pseudomonas*; *Enterobacteriaceae*; ?*Neisseria*; *Haemophilus*; *Moraxella*; *Pasteurella*; many atypicals. Essentially no anaerobic coverage.
  - **Useful in**: Pseudomonal infections; complicated UTIs; intra-abdominal infections
  - **Cipro XL** may not be rational choice → does not create high peak important in concentration-dependent killing.

- Levofloxacin (LEVAQUIN, g)
  - **250, 500, 750mg tab**
  - **NIHB** x 14 days maximum
  - **Coverage**: *Strep pneumoniae*; MSSA; *Enterobacteriaceae*; *Neisseria*; *Haemophilus*; *Moraxella*; *Pasteurella*; many atypicals; some anaerobes. Sometimes has activity against *Pseudomonas*, but unreliable.
  - **Useful in**: high-risk AECOPD; pneumonia (usually as alternative to 1st-line agents); intra-abdominal infections

- Moxifloxacin (AVELOX, g)
  - **400mg tab**
  - **NIHB** x 14 days maximum
  - **Coverage**: *Strep pneumoniae*; MSSA; *Enterobacteriaceae*; *Neisseria*; *Haemophilus*; *Moraxella*; *Pasteurella*; many atypicals; some anaerobes.
  - **Useful in**: high-risk AECOPD; pneumonia (usually as alternative to 1st-line agents). Does not penetrate urine – do not use to treat UTI.

- Norfloxacin (NOROXIN, g)
  - **400mg tab**
  - **NIHB** x 30 days maximum
  - **Coverage**: *Strep pneumoniae*; *Enterobacteriaceae*; *Neisseria*; *Haemophilus*; *Moraxella*; *Pasteurella*; many atypicals; some anaerobes.
  - **Useful in**: UTIs; prophylaxis of spontaneous bacterial peritonitis (prophylactic dose is 400mg po daily).
  - Appears equivalent to ciprofloxin in treatment of UTI.

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### Antifolates

- Prevent bacterial folate synthesis. Sulfamethoxazole & trimethoprim inhibit successive steps in folic acid pathway, & thus are synergistic in combination. Combination bactericidal; concentration-dependent killing.
  - **AE**: Generally well tolerated. **Common**: nausea, vomiting, skin reactions (photosensitivity; rash; pruritus; rare: SJS/TEN → 3 per 100,000 patients), ↑ headache, ↑ K, ↑ Na, ↑ SCR (often mild/ transient), ↑ BG.
  - **Rare**: bone marrow suppression, thrombocytopenia, hepatotoxicity (including hepatic necrosis), nephrotoxicity. Patients with HIV are more likely to have adverse reactions (rate as high as 25-50%).
  - **Reports of sudden death** (due to hyperkalemia) in elderly patients taking other drugs known to increase potassium (see DI section below).
  - **CI**: history of drug-induced immune thrombocytopenia from sulfonamides or trimethoprim; megaloblastic anemia from folate deficiency; severe liver disease; previous SJS from sulfonamides.
  - **Caution**: patients with G6PD deficiency (risk of hemolysis); patients with porphyria; infants < 2 months of age.

- **BACTRIM, SEPTRA, Cotrimoxazole, g**
  - **100/200mg (pediatric) tab**
  - **400/80mg (single strength) tab**
  - **800/160mg (double strength) tab**
  - **40/8mg per 1mL susp syrup**
  - **Coverage**: *Staphylococci* (often CA-MRSA); *Streptococcus pneumoniae*; *S. maltophilia*; *Moraxella*; *Haemophilus influenzae*; *Enterobacteriaceae*; *Shigella*; ?*Listeria*; *Burkholderia*; *Brucella*; *Pneumocystis*. *Strep pneumoniae* resistance = 7% in Canada (2013).↑
  - **Useful in**: UTI treatment or prophylaxis; skin and soft tissue infections; low-risk AECOPD; PJP prophylaxis.
  - **Rate of sulfamethoxazole and trimethoprim (5:1) calculated to achieve maximum synergistic effect.**
  - **Liquid suspension stable at room temperature. Excellent bioavailability.**

- **TROVAN, BACTRIM, SEPTRA, Cotrimoxazole, g**
  - **100, 200mg tab**
  - **Coverage**: Similar to cotrimoxazole combination, but not *Moraxella*.
  - **Useful in**: UTI treatment (only 3 days needed if uncomplicated); UTI prophylaxis
  - **Alternate to cotrimoxazole in sulfa allergy. Commonly used as monotherapy in Europe.**
  - **Alternate dosing of 200mg q24h an option. Excellent bioavailability.**
<table>
<thead>
<tr>
<th>Generic/Trade Name</th>
<th>Adverse Events</th>
<th>AE / Contraindications</th>
<th>CI / Drug Interactions</th>
<th>Dosing (Adult, Pediatric, Usual Max)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td><strong>Inhibits bacterial protein synthesis.</strong> Bacteriostatic; time-dependent killing. <strong>Coverage:</strong> Staphylococci; Streptococci; many oral anaerobes. Unreliable MRSA coverage and indoluble Staph &amp; Strep resistance.</td>
<td><strong>Useful in:</strong> skin and soft tissue infections; dental infections (although usually safer options). Reduces toxin production of Streptococci and Staphylococci (e.g. useful to toxic shock syndrome in necrotizing fasciitis – give in combination with penicillin).</td>
<td><strong>AE:</strong> nausea, diarrhea, rash (rare: SJS), ↑LTs. Rare: leukenopnia, thrombocytopenia. <strong>Higher risk of Clostridium difficile</strong> than other agents. <strong>AE profile plus increasing resistance</strong> (including inducible D-zone) limits role.</td>
<td><strong>Dosing:</strong></td>
<td><strong>Comments:</strong></td>
</tr>
<tr>
<td><strong>Peds:</strong> 10-30mg/kg/day po divided q6h</td>
<td><strong>Adult:</strong> 300-450mg po q6-8h</td>
<td><strong>Max:</strong> 1800mg/day</td>
<td><strong>$34</strong></td>
<td><strong>$25-30</strong></td>
<td><strong>$39</strong></td>
</tr>
<tr>
<td>Metronidazole</td>
<td><strong>Disrupts DNA of bacterial cells.</strong> Bactericidal. <strong>Coverage:</strong> most anaerobes, including anaerobic protozoa.</td>
<td><strong>Useful in:</strong> intra-abdominal infections; <strong>C difficile</strong>; bacterial vaginosis; trichomonal; diabetic foot infections; fistulizing Crohn’s disease (may help drainage).</td>
<td><strong>AE:</strong> GL upset, metallic taste, headache, vaginitis, peripheral/optic neuropathy (long-term use).</td>
<td><strong>Rare:</strong> neurotoxicity, leukenopnia, skin reactions (rash, pruritis, SJS/TEN).</td>
<td><strong>CI:</strong> Use of disulfiram in previous 2 weeks; alcohol during and 3 days after therapy.</td>
</tr>
<tr>
<td><strong>Dosing:</strong></td>
<td><strong>Peds:</strong> 2000mg x 1 dose</td>
<td><strong>Adult:</strong> 3000mg x 1 dose</td>
<td><strong>Max:</strong> 6000mg/day</td>
<td><strong>$234</strong></td>
<td><strong>$234</strong></td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td><strong>Damages bacterial DNA/proteins (bacteria convert nitrofurantoin into reactive forms). Multiple sites of attack</strong> lead to slow development. <strong>Coverage:</strong> Staphylococci; E. coli; Enterococcus faecalis; Citrobacter; Klebsiella.</td>
<td><strong>Useful in:</strong> <strong>First-line therapy in UTIs</strong> (only 5 days needed if uncomplicated). Avoid if suspected pyelonephritis.</td>
<td><strong>AE:</strong> Common: darkens urine, nausea, headache. Very rare: SJS/TEN.</td>
<td><strong>Max:</strong> 4000mg/day</td>
<td><strong>DI:</strong> May decrease effect of erythromycin (competitive binding to same bacteria protein site).</td>
</tr>
<tr>
<td><strong>Dosing:</strong></td>
<td><strong>Peds:</strong> 40mg/kg/day divided q6h</td>
<td><strong>Adult:</strong> 500mg po q6h if susceptible</td>
<td><strong>Max:</strong> 5000mg/day</td>
<td><strong>$38</strong></td>
<td><strong>$38</strong></td>
</tr>
<tr>
<td>Fosfomycin</td>
<td><strong>Inhibits cell-wall formation.</strong> Bactericidal. <strong>Coverage:</strong> 5-7- Staphylococci; Enterococci; Enterobacteriaceae.</td>
<td>Often coverage even if multi-drug resistance (MRSA, ESBL-producing organisms, VRE).</td>
<td><strong>Useful in:</strong> UTIs. Avoid if suspected pyelonephritis. Safe in pregnancy but usually better options.</td>
<td><strong>Max:</strong> 5000mg/day</td>
<td><strong>CI:</strong> Use of disulfiram in previous 2 weeks; alcohol during and 3 days after therapy.</td>
</tr>
<tr>
<td><strong>Dosing:</strong></td>
<td><strong>Peds:</strong> 15-30-50mg/kg/day po divided q8h</td>
<td><strong>Adult:</strong> 100mg MACRODANTIN po q12h with food</td>
<td><strong>Max:</strong> 200-400mg/day</td>
<td><strong>$18</strong></td>
<td><strong>$27-43</strong></td>
</tr>
<tr>
<td>Linezolid</td>
<td><strong>Inhibits bacterial protein synthesis.</strong> Usually bacteriostatic, but bactericidal against Streptococci. <strong>Coverage:</strong> Streptococci; Enterococci (including VRE); Staphylococci (including MRSA).</td>
<td><strong>Useful in:</strong> multi-drug resistant infections (including pneumonia, skin and soft tissue, etc.).</td>
<td><strong>DI:</strong> Use of disulfiram in previous 2 weeks; alcohol during and 3 days after therapy.</td>
<td><strong>Max:</strong> 600mg q12h</td>
<td><strong>CI:</strong> Use of disulfiram in previous 2 weeks; alcohol during and 3 days after therapy.</td>
</tr>
<tr>
<td><strong>Dosing:</strong></td>
<td><strong>Peds:</strong> 2000mg x 1 dose</td>
<td><strong>Adult:</strong> 600mg po q12h</td>
<td><strong>Max:</strong> 1200mg/day</td>
<td><strong>$38</strong></td>
<td><strong>$38</strong></td>
</tr>
<tr>
<td>Vancomycin</td>
<td><strong>Inhibits cell-wall formation.</strong> <strong>Coverage:</strong> The only oral use is for treatment of Clostridium difficile colitis (drug of choice if severe infection or, if second recurrence of <strong>C difficile</strong> infection; taper over ~8wks in recurrent infections).</td>
<td><strong>AE:</strong> rare when used po.</td>
<td><strong>Max:</strong> 125mg po q6h</td>
<td><strong>$234</strong></td>
<td><strong>$234</strong></td>
</tr>
</tbody>
</table>

**Methenamine mandelate MANDELAMINE** 500mg po q6h S33 [IF] | Creates acidic urine; indicated for UTI prophylaxis, but not first line (limited evidence); 21 likely ineffective in catheterized patients. | **AE:** rash, GL upset, bladder irritation, ↑LTs; **β-agonists, amphetamines, sulfonamides, acetazolamide, antacids; M:** Urinalysis, periodic LTs. | **Cl:** Severe hepatic dysfunction, gout. | **$19** | | **$19** |

**Useful Links:** Infectious Disease Society of America [www.idsoociety.org/IDSA_Practice_Guidelines](http://www.idsoociety.org/IDSA_Practice_Guidelines); Sanford Guide to Antimicrobial Therapy [www.sanfordguide.com](http://www.sanfordguide.com); Bugs & Drugs [www.bugsanddrugs.ca](http://www.bugsanddrugs.ca); RxFiles [www.RxFiles.ca](http://www.RxFiles.ca)| | | | | |

**Saskatchewan Antibiotics:** Regina [www.rqhealth.ca/clinical-support/Antibiograms/Saskatoon](http://www.rqhealth.ca/clinical-support/Antibiograms/Saskatoon); www.saskatoonhealthregion.ca/locations_services/Services/Pathology-Laboratory-Med/healthpractitioners/Pages/antibiograms.aspx | | | | | |

**Probiotics:** includes [Saccharomyces boulardii, Lactobacillus rhamnosus GG](http://www.sanfordguide.com), others. | [↓](http://www.sanfordguide.com) antibiotic-associated diarrhea; separate >2hrs from antibiotics. | **S. boulardii** 1g daily for **C difficile** diarrhea (caution: immunocompromised, pancreatitis). | | | |
The symptoms you presented with today suggest a VIRAL infection.

- Upper Respiratory Tract Infection (Common Cold): Lasts 7-14 days
- Flu: Lasts 7-14 days
- Acute Pharyngitis (“Sore Throat”): Lasts 3-7 days, up to ≤10 days
- Acute Bronchitis/”Chest Cold” (Cough): Lasts 7-21 days
- Acute Sinusitis (“Sinus Infection”): Lasts 7-14 days

You have not been prescribed antibiotics because antibiotics are not effective in treating viral infections, can cause side effects (e.g. diarrhea, yeast infections) and may even cause serious harm.

When you have a viral infection, it is very important to get plenty of rest and give your body time to fight off the virus.

**If you follow these instructions, you should feel better soon:**

- Rest as much as possible
- Drink plenty of fluids
- Wash your hands frequently
- Take over-the-counter medication, as advised:
  - Acetaminophen (e.g. Tylenol®) for fever and aches
  - Ibuprofen (e.g. Advil®) for fever and aches
  - Naproxen (e.g. Aleve®) for fever and aches
  - Lozenge (cough candy) for sore throat
  - Nasal spray (e.g. Salinex®, Flonase®, Nasacort® or Otrivin®) for nasal stuffiness. {NOTE: observe label directions; some products are problematic if overused!}
  - Other: ____________________________

**Please return to your provider if:**

- Symptoms do not improve in _____ day(s), or worsen at any time
- You develop a high fever (above 38°C, or _______ as directed)
- Other: ____________________________

Prescriber ____________________________

This “Viral Prescription Pad” has been adapted from the RQHR Antimicrobial Stewardship Program www.rqhealth.ca/antimicrobialstewardship, and is available in other languages. http://www.rxfiles.ca/rxfiles/uploads/documents/ABX-Viral-Prescription-Pad-Languanges.pdf
**We asked some clinicians: “How do you deal with patient expectations around antibiotics?”**

<table>
<thead>
<tr>
<th>PATIENT SAYS:</th>
<th>POSSIBLE CLINICIAN RESPONSE:</th>
<th>EVIDENCE AROUND REDUCING UNNECESSARY ANTIBIOTICS?</th>
<th>ADDITIONAL TIPS FOR GETTING PATIENT BUY-IN</th>
</tr>
</thead>
<tbody>
<tr>
<td>I feel really rotten!</td>
<td>Yes, I’m sure you do... and you look sick too, but feeling rotten doesn’t equal a bacterial infection. It’s most likely to be viral!</td>
<td>• Studies have demonstrated patient satisfaction with care for acute bronchitis depends most on physician-patient communication, not antibiotic treatment. iii, iv</td>
<td>➔ Use the term “chest cold” or “viral upper respiratory tract infection” as this makes it easier to convince patients they do not need antibiotics.</td>
</tr>
<tr>
<td>I really think I need something.</td>
<td>Yes, for sure. You need to stay home &amp; rest for a day. Here is an information hand-out and a script with options for symptom management.</td>
<td>• One study found that the duration of office visits for acute respiratory infection was only one minute longer when antibiotics were not prescribed. v</td>
<td>➔ Viruses commonly make you feel sick all over your body.</td>
</tr>
<tr>
<td>But, last time I got antibiotics!</td>
<td>In the past, we sometimes used antibiotics, they didn’t work, but the practice has given us “superbugs”!</td>
<td>• A change in antibiotic reimbursement resulted in fewer antibiotics prescribed, and a reduction in the level of antimicrobial resistance. vi</td>
<td>➔ Viruses are more easily spread from one person to another, so if you are the 3rd person in your house who’s sick... it’s probably a virus.</td>
</tr>
<tr>
<td>I drove and waited a long time. I don’t want to have to come back!</td>
<td>Yes. What I could do is give you a provisional prescription, good for a week. Don’t fill it now, but if all of the sudden you feel a lot worse, you can fill it without having to come in.</td>
<td>• A “watch and wait” prescription option ii</td>
<td>➔ Fever is how our bodies fight off any infection and not an indication of a bacterial infection.</td>
</tr>
<tr>
<td>I’ve been coughing for two weeks...</td>
<td>It’s pretty typical to cough for several weeks after a chest cold due to a virus. Would you like it if I gave you something to help with the cough?</td>
<td></td>
<td>➔ Colored nasal secretions do not equal a bacterial infection! Snot and sputum that becomes yellow/green is a sign your body is fighting off any infection.</td>
</tr>
<tr>
<td>I’ve been coughing steady, feverish, and feel like dying.</td>
<td>You do look quite unwell. It could just be a chest cold, but we should send you for an x-ray to rule out pneumonia and anything else.</td>
<td></td>
<td>➔ 70-80% of ear infections get better without antibiotics.</td>
</tr>
<tr>
<td>I think I’d like an antibiotic just in case. Can’t go wrong, right?</td>
<td>Actually, antibiotics cause a lot more side effects than we realize. There’s diarrhea, yeast infections, and occasionally some very serious harms. Plus, when we overuse, we increase the risk of resistant bacteria!</td>
<td></td>
<td>➔ Antibiotics do not reduce the duration of viral illness, but may cause harms (nausea, diarrhea, allergic reactions, etc.)</td>
</tr>
</tbody>
</table>

**ONE PHYSICIAN’S SCRIPT AROUND ACUTE BRONCHITIS**

I have examined you and I am happy there is no sign of serious illness, which would need an antibiotic today. Most chest colds get better on their own, although the cough may take several weeks to go away completely.

Antibiotics don’t seem to make much difference to how quickly most people recover. However, if you feel you are actually getting worse after awhile, taking antibiotics then may be reasonable.

So, here is an antibiotic prescription for you to keep at home. You are quite likely not to need it, but if your symptoms get noticeably worse, you can fill it within 7 days.

**TYPICAL SYMPTOM DURATION FOR SELECT VIRAL ILLNESS**

- Sore throat, pharyngitis: 6-10 days
- Cough, acute bronchitis: 2-3 weeks