Antibiotics & Common Infections

Stewardship, Effectiveness, Safety & Clinical Pearls

October 2016

ANTIMICROBIAL RELATED LINKS

CANADIAN GUIDELINES

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

MUMS Guidelines – "Orange Book" (Anti-infective Review Panel):
http://www.mumshealth.com

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).
http://www.dobugsneeddrugs.org/wp-content/uploads/info-sheet-english.pdf

4. Handouts for Patients
http://healthycanadians.gc.ca/drugs-products-medicaments-produits/buying-using-achat-utilisation/antibiotic-resistance-antibiotique/material-materiel/brochure-eng.php

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 pneumonia* (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

[1] http://www.cdc.gov/media/releases/2011/f0407_antimicrobialresistance.pdf

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.*" [i]
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, ...)
- ↑ risk of secondary fungal infections
- ↑ risk of an untreatable infection in the patient due to ↑ bacterial resistance

➡ To Society

- financial costs of treating adverse reactions (USA: $20 billion in excess healthcare costs) [1]
- 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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Acknowledgements (more details online)

RxFiles is very pleased to acknowledge those who contributed to Part 1 topic development & review.

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* Although many contributed to this topic workup, Lynette Kosar took the lead on the 4 primary therapeutic topic areas, including the overseeing related resident rotations. Well done Lynette!!!

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Coming up next, Spring 2017
ABX – Part 2:
Skin Infections, Acute Cystitis

www.RxFiles.ca

PEARLS for the MANAGEMENT of ACUTE UNCOMPLICATED BRONCHITIS

- **Antibiotics are NOT recommended**, as bronchitis is predominantly viral**.**
- Advise 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.

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.

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).

SYMPTOM MANAGEMENT — no quality evidence, but anecdotally may help

NONPHARM	• ↑/maintain hydration • ↑ humidity (e.g. PRN humidifier to maintain 30-50% humidity)	- No evidence for or against. - Hydration: caution in HF & CKD patients - Humidifier: clean frequently to ↓ risk of bacteria/fungi growth
	Honey 2.5 to 10mL po HS Not recommended in <1yr due to concerns with infant botulism	- No strong evidence for or against. - Cochrane review (3 RCTs, n=568): better than placebo, but inferior to dextromethorphan in ↓ cough frequency (cough duration not assessed).
COUGH SUPPRESSANTS	Dextromethorphan (DM) e.g. BENYLIN DM, ROBITUSSIN DM 10-30mg po q6-8hr PRN	- May ↓ number of coughing episodes but does not ↓ duration of illness. - Not recommended in children under 6 years of age due to safety & efficacy concerns. HEALTH CANADA
BRONCHODILATORS	Salbutamol VENTOLIN 100mcg 2 puffs inhaled QID	- 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).
	Ipratropium ATROVENT 20mcg 4 puffs QID	- Limited evidence (1 study, n = 14 for 3 weeks) in post-infectious cough. - May improve daytime & nighttime cough, & dyspnea associated with coughing.

- **Encourage prevention** e.g. smoking cessation, ↓ exposure to second-hand smoke.

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 **RCTs**=randomized controlled trials **TMP-SMX**=trimethoprim/sulfamethoxazole

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.

CRB-65	
Criteria	**Points**
Confusion: new onset based on a specific mental test, or disorientation to person, place or time	1
Respiratory rate ≥30 breaths/minute	1
Low **B**lood pressure: SBP <90mmHg or DBP ≤60mmHg	1
Age ≥ **65** years	1

Score	Risk of Mortality	Suggested Management
0	< 2%	• Outpatient
1-2	~9%	• Consider hospital admission
≥ 3	>19%	• Hospital admission

If a recent urea 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

PREVIOUSLY HEALTHY ADULT OUTPATIENT WITH NO RECENT ANTIBIOTIC USE

Most Common Bacterial Pathogen: Gram +ve: *Streptococcus pneumoniae*
Potential Pathogens: Atypical pathogens (*M. pneumoniae, C. pneumoniae)*

Doxycycline	200mg po Day 1, then 100mg po BID x 5-7 days	✓Based on SK antibiogram data [RQHR, SDCL, SHR], doxycycline has good activity against common/potential CAP pathogens (i.e. ***S. pneumoniae*** & **atypical pathogens**).
Amoxicillin may consider adding a macrolide if concerned about atypical pathogens (see Clinical Q&A)	1000mg po TID x 5-7 days Clarithromycin preferred if no major DIs e.g. warfarin, digoxin, statin, as may result in less resistance than azithro (t½). **Clarithromycin:** 500mg po BID x 5-7 days, or XL 1000mg po daily x 5-7 days **Azithromycin:** 500mg po daily x 3 days, or 500mg po Day 1, then 250mg daily x 4 days	**Amoxicillin:** ✓***S. pneumoniae*** (even intermediate susceptibility isolates) remain sensitive to high-dose amoxicillin. ✗ Does not cover **atypical pathogens**. See Clinical Q&A on whether atypical pathogen coverage is needed. **Macrolides:** ✓May be added to amoxicillin to cover **atypical pathogens**. ✗ There are concerns with using macrolides as monotherapy due to ↑ ***S. pneumoniae*** resistance. 2015 SK susceptibilities: RQHR 70%, SDCL 62%, SHR 80% (but 70% in 2014).

ADULT OUTPATIENT with COMORBIDITIES / ABX RESISTANT RISK FACTORS*

Most Common Bacterial Pathogen: Gram +ve: *S. pneumoniae*
Potential Pathogens: Gram –ve: *H. influenza, M. catarrhalis, K. pneumoniae*
Atypical pathogens: *M. pneumoniae, C. pneumoniae, Legionella*

Doxycycline	200mg po Day 1, then 100mg po BID x 5-7 days	✓ As above, & will also cover *S.aureus* & potential gram –ve pathogens.
Amox - Clav CLAVULIN may consider adding a macrolide re: atypical pathogens (see Clinical Q&A)	875mg po BID x 5-7 days see above macrolide options/dosing	**Amoxicillin - Clavulanate:** ✓ This category of patients may be at ↑risk of beta-lactam resistance, which is addressed with the addition of clavulanate to amoxicillin. ✗ Does not cover **atypical pathogens**. See Clinical Q&A on whether atypical pathogen coverage is needed. **Macrolides:** as above

Fluoroquinolones should be reserved for treatment failures, comorbidities with recent antibiotic use, allergies or documented infections with highly drug-resistant bacteria. Examples: levofloxacin [LEVAQUIN] 500-750 mg po once daily x 5 days
moxifloxacin [AVELOX] 400 mg po once daily x 5 days

***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 days); hospitalization or broad spectrum ABX in past 3 months; HIV/immunosuppressed.

+ve=positive **–ve**=negative **ABX**=antbiotic **AMOX-CLAV**=amoxicillin / clavulanate **BUN**=blood urea nitrogen **CAP**=community acquired pneumonia **CKD**=chronic kidney disease **CRB**=confusion, respiratory rate, blood pressure **C&S**=culture & sensitivity **DM**=diabetes mellitus **LOE**=level of evidence **pt**=patient **RQHR**=Regina Qu'Appelle Health Region **SDCL**=SK Disease Control Laboratory **SHR**=Saskatoon Health Region **SK**=Saskatchewan **tx**=treatment

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.

UNCOMPLICATED* CAP in PEDIATRIC OUTPATIENTS CPS 2015

Most Common Pathogens:

- **Infants & pre-school children:** viruses are the predominant cause
- **3 months to 5 years:** *S. pneumoniae;* viruses are still common
  - due to vaccination, typed *H. influenzae* as a causative pathogen is very rare CDN
- **>5 years:** *M. pneumoniae*, *C. pneumoniae*

FIRST LINE		
Amoxicillin	40-90mg/kg/day po ÷ TID (max 4g/day) x 7 - 10 days	• Provides best coverage of all beta-lactams against *S. pneumoniae* & **higher doses cover the majority of penicillin-resistant strains.** As such, high-dose should be used in RQHR**.**
PENCILLIN ALLERGY: TYPE IV HYPERSENSITIVITY (e.g. rash)		
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)	• 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	• Only use in patients ≥9 years old.
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)	• It is difficult for pediatric patients to produce a sputum sample. The majority of respiratory isolates are from tracheal suctions & antibiogram data likely does not represent pediatric outpatients. • Macrolide can be used empirically in patients with an anaphylactic penicillin allergy. If symptoms worsen or do not improve within 3-5 days, consider adding clindamycin (20-40mg/kg/day po ÷ TID).
Clarithromycin safety in <6 months is unknown	15mg/kg/day po ÷ BID x 7 - 10 days (max 500mg/dose)	

***uncomplicated =** acute, CAP in healthy immunized children without underlying pulmonary pathology aside from mild reactive airway disease

Duration of Therapy in Pediatrics: The standard duration remains 7-10 days (exception: azithromycin). One small study (n=140, ages 6 months to 5 years) in Israel concluded that 5 days was not inferior to 10 days, but 3 days was associated with ↑ failure rates.

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.
- Recommend a **PNEUMOVAX-23** vaccine for those ≥65 years of age, or at high risk regardless of age (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 ↓pneumonia-specific or all-cause mortality.
  - A **PNEUMOVAX-23** booster (>5 years) may be considered in high risk individuals, although data is limited and based on the theoretical ↓ in immunity over time.

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, &/or 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 McIssac) Score

Criteria	Points
Temperature > 38°C (>100.5 °F) oral temperature used in Centor score (adults)	1
Absence of cough	1
Swollen, tender anterior cervical nodes	1
Tonsillar swelling or exudate	1
Age 3 to 14 years	1
Age 15 to 44 years	0
Age ≥ 45 years	-1

Score	Risk of Streptococcal Infection	Suggested Management
-1 to 0	1 to 2.5%	- Symptomatic treatment - No RADT, culture or antibiotic needed
1	5 to 10%	
2	11 to 17%	- RADT or throat swab for culture. - If positive for GAS ⇨ antibiotic.
3	28 to 35%	
≥4	51 to 53%	

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 ↓ the risk of 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

FIRST LINE		
No antibiotic	- Majority of cases are viral. - Only use antibiotics in confirmed bacterial pharyngitis.	- See Symptom Management following page.
Penicillin V	Peds: ≤27 kg: 40mg/kg/day ÷ BID or TID x10 days (maximum 750mg/day) >27 kg & Adults: 300mg TID x 10 days, or 600mg BID x 10 days	- 1st line due to narrow spectrum of activity, efficacy, safety & low cost. - No documented resistance to GAS.
Amoxicillin	Peds: 40mg/kg/day ÷ BID or TID x10 days (maximum 1000mg/day) Adults: 500mg BID x 10 days	Compared to penicillin: - broader spectrum than required; as effective - liquid more palatable for children ☺
PENICILLIN ALLERGY: TYPE IV HYPERSENSITIVITY (e.g. rash)		
Cephalexin	Peds: 25-50mg/kg/day ÷ BID or QID x10 days (maximum 1000mg/day) Adults: 250mg QID x 10 days, or 500mg BID x 10 days	- No documented resistance to GAS.
PENICILLIN ALLERGY: TYPE I HYPERSENSITIVITY (i.e. anaphylaxis)		
Do not use the following antibiotics unless confirmed GAS & confirmed type I reaction to penicillin, due to concerns with ↑resistance to macrolides & adverse events e.g. *C. diff.*		
Clindamycin	Peds: 20mg/kg/day ÷ TID x10 days (maximum 900mg/day) Adults: 300mg TID x 10 days	**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).
Clarithromycin	Peds: 15mg/kg/day divided BID x10 days (maximum 500mg/day) Adults:250mg BID x 10 days	
Erythromycin	Peds: 40mg/kg/day ÷ BID or TID x10 days (maximum 2000mg/day) Adults:250mg QID x 10 days	
Azithromycin	Peds: 12mg/kg/day daily x 5 days, or 20mg/kg/day daily x3 days (max 500mg/d) Adults: 500mg Day 1, 250mg x Days 2-5, or 500mg daily x 3 days	

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

SYSTEMIC ANALGESICS	e.g. Ibuprofen ADVIL, g Peds: 5-10 mg/kg po q6-8hr PRN (maximum 40mg/kg/day) Adults: 400mg po q6-8hr PRN	- Ibuprofen ↓ associated pain more than acetaminophen & placebo. - Reduces fever.
	Acetaminophen TYLENOL, g Peds: 10-15mg/kg po q4-6hr PRN (maximum 75 mg/kg/day) Adults: 1000mg po q4-6hr PRN	- Less effective than NSAIDs for ↓ associated pain but more effective than placebo. - Reduces fever.
MEDICATED LOZENGES	Benzocaine CEPACOL ES, CHLORASEPTIC 10mg lozenge q2hr PRN	- Alleviates throat pain if used frequently. - Avoid in children due to: ▪ risk of choking ▪ concerns with methemoglobinemia
MEDICATED SPRAYS	Phenol CHLORASEPTIC 5 sprays q2hr PRN	- No evidence, but anecdotally may provide relief from associated pain.
RINSES	• Gargling or drinking warm liquids e.g. warm salt water rinse, tea • Benzydamine TANTUM, PHARIXIA 15mL gargle or rinse q1.5-3hr PRN	- Little evidence, but anecdotally provide relief from associated pain.

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 herbals: 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
  - wait to prescribe antibiotics until the results of the throat swab are available
    - starting antibiotics within 9 days of symptom onset prevents acute rheumatic fever
    - if antibiotics are started empirically, discontinue if throat swab is negative
    - children are at a greater risk of complications (e.g. otitis media, peritonsillar abscess, rheumatic fever); 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).

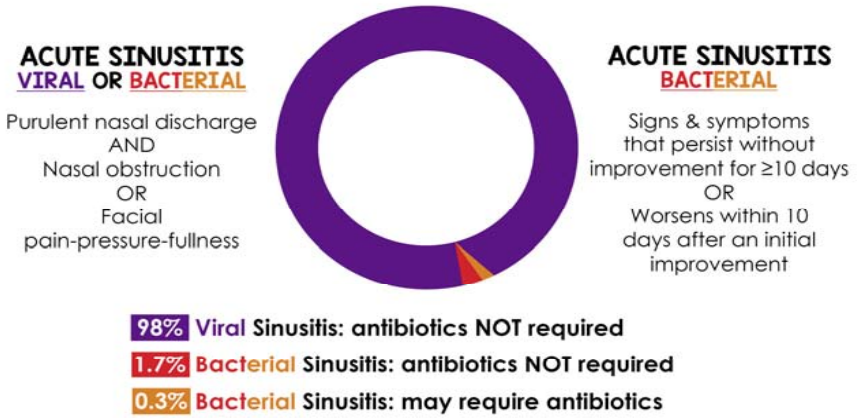
Abbreviations:
GAS=Group A Streptococcus **IDSA**=Infectious Diseases Society of America **NSAID**=non-steroidal anti-inflammatory drug **NNT**=number needed to treat **RADT**=rapid antigen detecting test

PEARLS 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.



- 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.[AAO-HNS'15, IDSA'12, CSO-HNS'11]
- 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 continued

- 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.

SYMPTOM MANAGEMENT

ANALGESICS	• Acetaminophen TYLENOL, g - 10-15mg/kg q4-6hr PRN (max 75mg/kg/day) - 1000mg po q6hr PRN (max 3.2-4g/day) • Ibuprofen ADVIL, g - 5-10mg/kg q6-8hr (max 40mg/kg/day) - 400mg po q6-8hr PRN	- No quality evidence but should reduce fever & treat localized pain.
DECONGESTANTS	• Xylometazoline OTRIVIN (≥12 yrs & adults): 2-3 sprays/nostril q8-10hr PRN • Pseudoephedrine: SUDAFED - 6-11yrs: 30mg po q4-6hr PRN (max 120mg/d) - ≥12 yrs & adults: 60mg po q4-6hr PRN, or 120mg ER po q12h PRN	- Limited evidence with xylometazoline. - May relieve congestion & promote sinus drainage. - Topical preparations: less systemic absorption (oral AE: CV, insomnia); limit to 3-5 days to prevent rebound symptoms
CORTICOSTEROIDS	**INTRANASAL** (not recommended in <3yrs) • Fluticasone FLONASE, g 50 mcg 2 sprays in each nostril once daily • Mometasone NASONEX, g 50 mcg 2 to 4 sprays each nostril twice daily **ORAL** (only for severe sinusitis) • 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). - **ORAL:** may provide benefit for **severe** sinusitis, in combination with an antibiotic (NNT=7 for symptom improvement or resolution). No benefit with monotherapy.
NONPHARM	• warm facial packs	- No quality evidence but anecdotally may promote mucus drainage.
	• saline nasal drops/rinses/irrigation - 150mL hypertonic saline nasal irrigation NETI POT daily - Saline spray SALINEX 1 spray TID-QID PRN	- Anecdotally, nasal drops/sprays may help. - Limited conflicting evidence with nasal irrigation; may ↓symptoms, ↑quality of life, ↑mucociliary clearance & ↓use of other sinusitis medications.

Is watchful waiting an appropriate option for patients with acute sinusitis?

- Most sinusitis cases improve without antibiotics. Watchful waiting should be considered in patients who:
  - present with symptoms that have not worsened, or
  - have had symptoms for less than 10 days, and
  - you feel confident in their ability for follow-up (i.e. antibiotic will be started if the acute sinusitis symptoms fails to improve after 7 days or worsen at any time)
- Write a prescription that is post-dated for when therapy may be initiated, & instruct the patient to call and inform the clinic if they fill the prescription.

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)		
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.
SEVERE (fever ≥39°C AND purulent nasal discharge or facial pain x 3-4 days) or TREATMENT FAILURE WITH AMOXICILLIN (symptoms not resolved after 3-5 days)		
Amoxicillin / Clavulanate CLAVULIN 4:1 or 7:1 ratio Dose listed as per amoxil component	45mg/kg/day CLAVULIN ÷ BID x 10 days (±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*	- 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 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	

*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: t½).

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.

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

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

Abbreviations:
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

Important Definitions

- **Minimum Inhibitory Concentration (MIC)**: the lowest concentration of an antimicrobial that prevents bacterial growth, but does not kill the organism.
- **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-**p**ositive bacteria appear **p**urple 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*, *Chlamydophila*, *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, fluroquinolones, 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. Cloxacillin 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 of ≥ 1 of the following → severe COPD or worse (i.e. FEV < 50%); ≥ 4 exacerbations per year; ischemic heart disease; use of home O_2; 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.

Quick References

Antibiotics During Pregnancy/Lactation

Safe / Likely Safe / Caution / Contraindicated

			1st Trimester	2nd Trimester	3rd Trimester	Lactation
FLUOROQUINOLONES			? malformations	safer alternatives usually available		
MACRO	Erythromycin – non-estolate					
MACRO	Erythromycin estolate **ILOSONE**		risk of maternal hepatotoxicity			
MACRO	Azithromycin / Clarithromycin					
PEN	Amoxicillin ± clav / Ampicillin		?cleft lip/palate ≤0.4%			(with clavulanate)
PEN	Cloxacillin / Penicillin V					
CEPHALOSPORINS						
TETRACYCLINES			abnormal teeth & bone development, malformations, maternal hepatotoxicity			tetracycline
						doxy-, mino-cycline
OTHERS	Clindamycin					
OTHERS	Cotrimoxazole **SEPTRA, BACTRIM**	Sulfamethoxazole			hemolytic anemia, neonate jaundice, kernicterus	ok in healthy term infants without G6PD deficiency
OTHERS		Trimethoprim	↓ folic acid			
OTHERS	Metronidazole (oral)		1st trimester: accumulated data suggests likely safe			may hold breastfeeding 12-24hr post tx
OTHERS	Nitrofurantoin				neonate hemolytic anemia	avoid in infants 8 d to 1 mons & G6PD deficiency
OTHERS	Vancomycin					

Cephalosporin Generations (available in Canada)

1st	2nd	3rd	4th
cephalexin (po)	cefuroxime (po/IV/IM)	cefixime (po)	cefepime (IV/IM)
cefadroxil (po)	cefprozil (po)	ceftriaxone (IV/IM)	
cefazolin (IV/IM)	cefaclor D/C (po)	ceftazidime (IV/IM)	
	cefoxitin (IV/IM)	cefotaxime (IV/IM)	

In penicillin-allergic patients, how likely is cephalosporin cross-sensitivity?

- 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 cefprozil or cephalexin; penicillin with cefoxitin.)
- 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.[1,7]

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).

✗ =Non-Formulary in SK ☎=Exception Drug Status in SK ⊗=not covered by NIHB ▼=covered by NIHB ☺=tastes good ❄ =refrigerate after reconstitution **abx**=antibiotics **AECOPD**=acute exacerbation of COPD **BG**=blood glucose **CA-MRSA**=community-associated MRSA **CBC**=complete blood count **CSF**=cerebrospinal fluid **ESBL**=extended spectrum beta-lactamase **FEV1**=forced expiratory volume in 1 second **GI**=gastrointestinal **HIV**=human immunodeficiency virus **INR**=international normalized ratio **LFT**=liver function tests **MAC**=mycobacterium avian complex **MIC**=minimum inhibitory concentration **MRSA**=methicillin-resistant *Staphylococcus aureus* **MSSA**=methicillin-sensitive *Staphylococcus aureus* **OR**=odds ratio **PJP**=pneumocystis jirovecii pneumonia **PK**=pharmacokinetics **PRSP**=penicillin resistant *Streptococcus pneumonia* **SJS**=Stevens Johnson syndrome **SMX/TMP**=sulfamethoxazole/trimethoprim **TEN**=toxic epidermal necrolysis **UTI**=urinary tract infection **VRE**=vancomycin resistant enterococcus

Generic/TRADE	Adverse Events AE / Contraindications CI / Drug Interactions DI / Monitor M / Comments	Dosing (Adult, Pediatric, Usual Max)	$/10d
Penicillins: Binds to penicillin binding proteins on bacterial cell walls, inhibiting cell wall biosynthesis. Bactericidal. Demonstrates time-dependent killing. • AE: rash, nausea, vomiting, diarrhea, melanoglossia. **Rare**: allergic reactions, cytopenias, acute interstitial nephritis. Aminopenicillins (amoxicillin, ampicillin) ↑ risk of SJS (but rare → 2-3 per 100,000 patients).[6] • DI: can ↑INR with warfarin; ?may cause oral contraceptive failure. M: signs of anaphylaxis. True penicillin anaphylactic allergy: 0.01% of population. PK: Amoxicillin and amox/clav have excellent bioavailability.			
Amoxicillin AMOXIL, g 125, 250mg chew tab cherry 25, 50mg/mL susp strawberry, banana, sugar free, berry ☺ ❄ 250, 500mg cap P1,P2,3 L 1st trimester: ?cleft 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. *Strep pneumo* resistance only 3% in Canada for community-treated infections.[4] • High pediatric doses (e.g. 90mg/kg/day) can overcome moderate *Strep pneumo* resistance in acute otitis media & community acquired pneumonia. Risk factors for PRSP: recent antibiotic use, daycare, not given PREVNAR. • Consider watchful waiting in acute otitis media for suitable children (see page 78). • Excellent bioavailability. Achieves high concentrations in the middle ear.	**Peds**: 40-50mg/kg/day divided q8-12h 75-90mg/kg/day divided q8-12h if risk of *Strep pneumo* resistance max 3g/day **Adult**: **500**-1000mg po q8h **Max**: 1000-4000mg/day	$17 $22-32 $40
Amox/Clavulanate CLAVULIN, g • Strength listed is **amoxicillin** component. 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 NNH=10.[2,3] Less diarrhea with q12h dosing vs q8h. P1,P2,3 L	**Amox:clav ratio →** **2:1 (tab) q8h $23** • **Adults**: 250mg tab q8h • Often for less serious infections, or renal dysfunction (q12-24h). • Note: two 250mg tabs are not equal to one 500mg tab **4:1 (tab, susp) q8h $23-27** • **Adults**: 500mg tab q8h • **Peds**: 25, 50mg/mL susp ❄ rasp-orange dosed at 20-40mg/kg/day divided q8h **7:1 (tab, susp) q12h $23** • **Adults**: 875mg tab q12h • **Adults**: may give 875mg of suspension q12h if difficulty swallowing • **Peds**: 40, 80mg/mL susp rasp-orange ❄ dosed at 45mg/kg/day divided q12h **14:1 (combo) q12h $69** **Peds**: Use when targeting 90mg/kg/day in PRSP: -45mg/kg/d plain amoxicillin PLUS -45mg/kg/d amox-clav 7:1 susp **Decreased diarrhea** with ratios e.g. **7:1** that allow for **q12h** (3.4% vs q8h 5.9%).[2]		
Ampicillin, g 250, 500mg cap P1,P2,3 L 1st trimester: see amoxicillin	• **Coverage**: *Streptococci*; *Enterococcus faecalis*; *Listeria*; *N. meningitidis*. [Same spectrum as amoxicillin.] • **Useful in**: some UTIs with sensitive enterococcus; meningitis (IV formulation, as part of combo therapy). • **Disadvantages vs amoxicillin**: ↓ absorption, ↓ convenience (q6h), & ↑ AE (diarrhea, due to incomplete absorption). Good CSF penetration. Useful in severe listeria infections due to availability of an IV formulation.	**Peds**: 50-100mg/kg/day divided q6h **Adult**: 500mg po q6h **on empty stomach** **Max**: 2000mg/day	$26 $45 $45
Cloxacillin, g 25mg/mL susp cherry ❄ 250, 500mg cap P L	• **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.	**Peds**: 50-100mg/kg/day divided q6h **Adult**: 500mg po q6h **on empty stomach** **Max**: 4000mg/day	$111 $72 $134
Penicillin V Potassium PEN-VK, g 25mg/mL sol'n fruity ❄ 60mg/mL sol'n fruity ✗ ▼ ❄ 300mg (480,000 unit) tab P L	• **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.	**Peds**: 25-50mg/kg/day divided q6-12h **Adult**: 300-600mg po q6h **on empty stomach** 600mg po q12h option in pharyngitis **Max**: 3000mg/day	$31 $19 $22
Cephalosporins: Binds to penicillin binding proteins on bacterial cell walls, inhibiting cell wall biosynthesis. Bactericidal. Demonstrates time-dependent killing. Gram-negative coverage increases as generation increases. All cephalosporins lack coverage of *Listeria*, atypicals, MRSA, & *Enterococci* (**LAME**). Gonorrhea resistance to cefixime ~ 2% in Canada (combine cefixime with a macrolide due to resistance + to add chlamydia coverage).[4,5] • AE: rash, nausea, diarrhea. **Rare**: allergic reactions, cytopenias. • DI: can ↑INR with warfarin; ?may cause oral contraceptive failure. M: signs of anaphylaxis. Risk of allergy cross-sensitivity between cephalosporins and penicillins is low - see Antibiotic Overview page.			
Cephalexin KEFLEX, g 25, 50mg/mL orange-banana ☺ ❄ 250, 500mg tab P L	• 1st-generation cephalosporins. • **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.	**Peds**: 25-100mg/kg/day po divided q6h **Adult**: 500mg po q6h (max 4000mg/day)	$29 $30-50
Cefadroxil 500mg cap ✗ ▼ P L DURICEF, g		**Peds**: 30mg/kg/day po divided q6h **Adult**: 500mg po q12h (max 1000mg/day)	$30 $30
Cefprozil CEFZIL, g 25, 50mg/mL susp bubblegum ☺ ❄ 250, 500mg tab P L	• 2nd-generation cephalosporins. • **Coverage**: *Streptococci*; MSSA; *Moraxella*; *Haemophilus influenzae*; *Proteus*; *E. coli*; *Klebsiella*. (H PEK) • **Useful in**: low-risk AECOPD; community-acquired pneumonia. • Cefuroxime has poor bioavailability (37% fasting; 52% with food). Cefprozil has excellent bioavailability.	**Peds**: 15-30mg/kg/day po divided q12h **Adult**: 500mg po q12h (max 1000mg/day)	$18 $29
Cefuroxime axetil CEFTIN, g 25mg/mL susp, 250mg sachet tutti-fruiti ❄ 250, 500mg tab P L		**Peds**: 20-30mg/kg/day po divided q12h **Adult**: 500mg po q12h **with food** (max 1g/d)	$29 $42
Cefixime SUPRAX, g 20mg/mL susp strawberry ☺ 400mg tab P L	• 3rd-generation cephalosporin. **Coverage**: *Streptococci*; *Moraxella*; *Haemophilus influenzae*; ?*Enterobacter*; *Neisseria*; *Proteus*; *E. coli*; *Klebsiella*; *Serratia*. (HEN PECKS) • **Useful in**: gonorrhea (800mg po x1 dose + azithro); pyelonephritis or complicated UTIs; low-risk AECOPD.	**Peds**: 8mg/kg po q24h **Adult**: 400mg po q24h **Max**: 400mg/day	$29 $44 $44
Ceftriaxone Injection ROCEPHIN, g 1, 2, 10g vials for injection (IM/IV) ✗ ⊗ P L	• 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 gonorrhea; initial treatment of suspected pyelonephritis while waiting for cultures).	**Peds**: 50mg/kg IM/IV q24h **Adult**: 1000-2000mg IM/IV q24h **Max**: 2000mg/day	$23-46 (1 dose)

Discontinued Products: Penicillin V Benzathine PEN-VEE suspension; cefaclor CECLOR tablet

Generic/TRADE	Adverse Events AE / Contraindications CI / Drug Interactions DI / Monitor M / Comments	Dosing (Adult, Pediatric, Usual Max)	$/10d
Macrolides: Inhibits bacterial protein synthesis. Bacteriostatic. Demonstrates time-dependent killing. Reserve when possible; useful for Streptococcal infections in context of beta-lactam allergy. • **AE**: GI upset (erythromycin highest incidence); QT prolongation (clarithromycin = erythromycin > azithromycin); ↑LFTs; headache; insomnia. **Rare**: ototoxicity, infantile hypertrophic pyloric stenosis. • **CI**: Caution in myasthenia gravis (possible association with muscle weakness). • **DI**: Clarithromycin and erythromycin CYP3A4 & p-glycoprotein inhibitors (clarithromycin > erythromycin) → increased levels of alfuzosin, alprazolam, amitriptyline, amiodarone, apixaban, calcium channel blockers, colchicine, digoxin, haloperidol, midazolam, paroxetine, quetiapine, risperidone, rivaroxaban, sertraline, statins (atorva-, simva-, lova-statin), tamsulosin, tolterodine, warfarin, & others. See RxFiles Drug Interactions. • **M**: LFTs, CBC (with prolonged therapy) • No coverage of MRSA. Minimal CNS penetration. *Streptococcus pneumoniae* resistance in SK (2015) ≈ 20-30%; in Canada (2013) ≈ 25%.[4] Increased doses do not overcome *Streptococcus pneumoniae* resistance.		
Azithromycin ZITHROMAX, g 20, 40mg/mL susp cherry ☺ ❄ 250mg tab 600mg tab ✗ ▼ After reconstitution, suspension may be kept at room temperature.	• **Coverage**: *Streptococci*; *N. gonorrhoeae*; *Moraxella*; *Haemophilus influenzae*; *Legionella*; many atypicals. • **Useful in**: pneumonia; upper respiratory tract infections; low-risk AECOPD; sexually transmitted infections including chlamydia and gonorrhea; MAC prophylaxis in HIV pts; cat-scratch disease; travelers' diarrhea (in kids, or travel to Asian countries). • Long half-life → 5 day treatment ≈ 10 days therapeutic levels. • 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 → 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 ↓ pulmonary inflammation – but efficacy is limited).	**Peds**: 10mg/kg day 1; 5mg/kg days 2-5 or 20mg/kg daily x 3 days **Adult**: 500mg day 1; 250mg days 2-5 500mg daily x 3 days in bacterial sinusitis & others **Max**: 500mg/day Gonococcal STI therapy: azithromycin 1000mg stat + cefixime 800mg stat (or ceftriaxone IM x1 if anogenital, pharyngeal infection, or in men who have sex with men)	$21 $19 $24
Clarithromycin BIAXIN, g 25, 50mg/mL susp fruity 250, 500mg tab 500mg XL tab	• **Coverage**: *Streptococci*; *Moraxella*; *Haemophilus influenzae*; *Legionella*; many atypicals. • **Useful in**: pneumonia; upper respiratory tract infections; low-risk AECOPD; MAC prophylaxis in HIV pts (but DIs with HIV medications possible). • Keep reconstituted suspension at room temperature. • XL tab = with food & once daily. Regular tab = with or without food.	**Peds**: 15mg/kg/day po divided q12h **Adult**: 500mg po q12h (or 1000mg XL daily cc) **Max**: 1000mg/day	$24 $28-38
Erythromycin, g **ERYC** 250, 333mg cap **Erythromycin base** 250mg tab **Erythromycin Stearate** 250mg tab (500mg ✗ ▼) **Erythromcyin 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.) • **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.[11] • **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. • **ERYC** may be sprinkled on food. • Erythromycin unsafe in porporhyria.	**Peds (Estolate)**: 30-40mg/kg/day divided q6h **ERYC**: 333mg po q8h **Base**: 250mg po q6h **Stearate**: 250mg po q6h **Max**: 2000mg/day	$21 $33 $23 $20 $29-34
Tetracyclines: Inhibits bacterial protein synthesis. Bacteriostatic. *Streptococcus pneumoniae* resistance ≈ 10% in Canada (2013).[4] • **AE**: **Common**: GI upset (DOX = MIN < TET), vaginal candidiasis, photosensitivity (DOX > TET > MIN; esp. UVA, & dose-dependent i.e. less of a problem at DOX 100mg/day). Use Sunscreen SPF 15-30, especially if long-term use. Sit up after taking for at least 30 minutes, and take with a full glass of water, to reduce risk of pills lodging in the esophagus and causing ulceration. MIN: hyperpigmentation of skin (rare bluish skin) & mucous membranes, lightheadedness, dizziness, vertigo, ataxia, drowsiness & fatigue. **Serious**: rare azotemia, pseudotumor cerebri (benign intracranial hypertension). MIN: rare lupus-like reaction, autoimmune hepatitis & hypersensitivity syndrome (case reports; implicated far more often in hypersensitivity reactions than other tetracyclines). • **CI**: Pregnancy, Children < 9yrs, severe renal or hepatic dysfunction; DOX: myasthenia gravis (possible association with muscle weakness). • **DI**: ↓ GI absorption: Fe^{++}, bismuth, Al^{+++}, Ca^{++}, Mg^{++} (separate dose by 2 hr); ↑INR and bleeding risk with warfarin; may ↓ oral contraceptive effectiveness; isotretinoin (intracranial hypertension/hemorrhage). • **M**: if using MIN long-term, consider LFTs & antinuclear factor baseline & q3-4 months.		
Doxycycline = DOX DOXYCIN, g 100mg cap, tab	• **Coverage**: Broad spectrum agent → *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; ricketssia; 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.	**Peds ≥9 yrs**: 2-5mg/kg/day divided q12h **Adult**: 200mg stat, then 100mg q12h or 200mg stat, then 100mg daily **Max**: 200mg/day	$23 $23 $17 $23
Minocycline = MIN MINOCIN, g 50, 100mg cap	• **Coverage**: Broad spectrum agent → *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).	**Peds ≥9**: 4mg/kg stat; then 4mg/kg/d ÷ q12h **Adult**: 200mg x 1; then 100mg po q12h **Max**: 200mg/day	$24 $24 $24
Tetracycline = TET TETRACYN, g 250mg cap	• **Coverage**: Broad spectrum agents → *Staphylococci*; *Strep pneumoniae*; *Moraxella*; *Haemophilus influenzae*; many atypicals; many anaerobes including spirochetes. • **Useful in**: acne; actinomycosis; periodontitis. • **Take TET on empty stomach** - absorption is ↓ by food & dairy.	**Peds ≥9 yrs**: 25mg/kg/day divided q6h **Adult**: 250mg po q6h **on empty stomach** **Max**: 2000mg/day	$13 $13 $17

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

Generic/TRADE	Adverse Events AE / Contraindications CI / Drug Interactions DI / Monitor M / Comments	Dosing (Adult, Pediatric, Usual Max)	$/10d

Fluoroquinolones: Inhibits DNA-gyrase, causing breakdown of bacterial DNA. Bactericidal. Concentration dependent killing (aim for high peak concentrations).

- **AE**: 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.
- **DI**: CYP1A2 inhibition → ↑levels of clozapine, duloxetine, methotrexate, quinapril, rasagiline, ropinirole, theophylline, tizanidine, varenicline, ↑INR with warfarin. QT prolongation (watch for other QT-prolonging agents).
- ↓ absorption via chelation with Ca^{++}, Fe^{++}, Al^{+++}, Mg^{++} (may space calcium, iron, multivitamins, etc. by giving >2 hours after fluoroquinolone, or hold for duration of fluoroquinolone therapy). Binds to enteral tube feeds (due to cations in feed - calcium, iron, etc.). May have less absorption via jejunostomy tube since fluroquinolones are likely absorbed in the duodenum. Increased risk of tendon rupture when given with corticosteroids.
- **CI**: See adverse effects. Safety < 18 years not proven (but ciprofloxacin in particular often used). **M**: If prolonged therapy: CBC, SCr, LFTs. **PK**: ciprofloxacin, levofloxacin, moxifloxacin = excellent bioavailability.
- Moxifloxacin and levofloxacin → anaerobic, atypical, *Streptococci*, & gram-negative coverage has lead to designation as "respiratory fluoroquinolones"; effective in pneumonia and AECOPD, **but reserve use** where possible.

Reserve fluoroquinolones whenever possible.

Why?

- These are broad-spectrum agents, with particularly good coverage against gram-negative pathogens. Preventing resistance, by limiting fluoroquinolone use, is important.
- Ciprofloxacin has reliable antipseudomonal activity; agents that kill *Pseudomonas* are uncommon. Note: if *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.

Ciprofloxacin CIPRO, g 250, 500, 750mg tab ☎ ▼ 500mg XL tab, g ☎ ⊗; 1000mg XL tab ☎ ⊗ 100mg/mL susp ☎ ▼ strawberry	• **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.	**Peds**: 20-30mg/kg/day po divided q12h **Adult**: 500mg po q12h (or 1000mg XL daily) separate from dairy **Max**: 1500mg/day	$29 $26 $33
Levofloxacin LEVAQUIN, g 250, 500, 750mg tab ☎ ▼ NIHB x 30 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	**Peds**: 8-10mg/kg po q24h **Adult**: **500**-750mg po q24h separate from dairy **Max**: 750mg/day	$31 $29-45 $45
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 UTIs.	**Peds**: not indicated **Adult**: 400mg po q24h separate from dairy **Max**: 400mg/day	- $28 $28
Norfloxacin NOROXIN, g 400mg tab ☎ ▼	• **Coverage**: *Strep pneumoniae*; MSSA; *Enterobacteriaceae* • **Useful in**: UTIs; prophylaxis of spontaneous bacterial peritonitis (prophylactic dose is 400mg po daily). • Appears equivalent to ciprofloxacin in treatment of UTI.[8-10]	**Peds**: not indicated **Adult**: 400mg po q12h separate from dairy **Max**: 800mg/day	- $23 $23

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),[6] 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%).[12] Reports of sudden death (due to ?hyperkalemia) in elderly patients taking other drugs known to increase potassium (see DI section below).[13-14]
- **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.
- **DI**: 2C9 inhibitor, 3A4 substrate: ↑levels of carvedilol, digoxin, phenytoin; ↑INR and bleed risk with warfarin. ↑hypoglycemia risk with hypoglycemic agents (e.g. gliclazide, insulin). Levels of cotrimoxazole ↓ by 3A4 inducers (e.g. carbamazepine, phenobarb, phenytoin, rifampin). ↑hyperkalemia risk with >3-5d of therapy, elderly, CKD, HF, DM, meds ↑K^+ (e.g. ACEI, ARB, spironolactone, eplerenone, NSAIDs, prednisone).
- **M**: CBC, K^+ (if >3-5d of therapy), SCr, BUN.

Sulfamethoxazole/Trimethoprim BACTRIM, SEPTRA, Cotrimoxazole, g 100/20mg (pediatric) tab 400/80mg (single strength) tab 800/160mg (double strength) tab 40/8mg per 1mL susp cherry	• **Coverage**: *Staphylococci* (& often CA-MRSA); *Streptococcus pneumoniae*; *S. maltophilia*; *Moraxella*; *Haemophilus influenzae*; *Enterobacteriaceae*; *Shigella*; ?*Listeria*; *Burkholderia*; *Brucella*; *Pneumocystis*. *Strep pneumo* resistance ≈ 7% in Canada (2013).[4] • **Useful in**: UTI treatment or prophylaxis; skin and soft tissue infections; low-risk AECOPD; PJP prophylaxis. • Ratio of sulfamethoxazole and trimethoprim (5:1) calculated to achieve maximum synergistic effect. • Liquid suspension stable at room temperature. Excellent bioavailability.	**Peds**: 6-12mg/kg/day TMP po divided q12h **Adult**: 800/160mg po q12h **Max**: 320mg/day of TMP component {Note, high dose SMX-TMP 1600/320mg q12h studied recently in skin infections, but drainage is still mainstay of therapy}	$21 $13 $13
Trimethoprim PROLOPRIM, g 100, 200mg tab	• **Coverage**: Similar to cotrimoxazole combination, but not *Moraxella*. • **Useful in**: UTI treatment (only 3 days needed if uncomplicated); UTI prophylaxis • Alternative to cotrimoxazole in sulfa allergy. Commonly used as monotherapy in Europe. • Alternate dosing of 200mg q24h an option. Excellent bioavailability.	**Peds**: 10mg/kg/day po divided q12h **Adult**: 100mg po q12h **Max**: 200mg/day	$17 $17 $17

Discontinued Products: Gemifloxacin **FACTIVE** tab; Ofloxacin **FLOXIN** tab; Trovafloxacin **TROVAN** tab [hepatic adverse events]; Gatifloxacin **TEQUIN** tab [increased diabetes]; Grepafloxacin **REXAR** tab [increased cardiac events]

Generic/TRADE	Adverse Events AE / Contraindications CI / Drug Interactions DI / Monitor M / Comments	Dosing (Adult, Pediatric, Usual Max)	$/10d
Clindamycin DALACIN C, g 150, 300mg cap 15mg/mL sol'n cherry DO NOT REFRIGERATE Excellent bioavailability P L	• Inhibits bacterial protein synthesis. Bacteriostatic; time-dependent killing. **Coverage**: *Staphylococci*; *Streptococci*; many oral anaerobes. Unreliable MRSA coverage and inducible *Staph* & *Strep* resistance. • **Useful in**: 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). • **AE**: nausea, diarrhea, rash (rare: SJS), ↑LFTs. Rare: leukopenia, thrombocytopenia. Higher risk of *Clostridium difficile* than other agents. AE profile plus increasing resistance (including inducible *D-zone*) limits role. • **DI**: May decrease effect of erythromycin (competitive binding to same bacteria protein site). • **M**: Signs of *Clostridium difficile* infection (watery diarrhea ≥3 times/day); CBC, LFTs, & SCr if prolonged therapy.	**Peds**: 10-30mg/kg/day po divided q6h **Adult**: 300-450mg po q6-8h **Max**: 1800mg/day	$34 $25-30 $39
Metronidazole FLAGYL, g 250mg tab 500mg cap ✗ ▼ Excellent bioavailability P_1,$P_{2,3}$ L	• Disrupts DNA of bacterial cells. Bactericidal. **Coverage**: most anaerobes, including anaerobic protozoa. • **Useful in**: intra-abdominal infections; *C. difficile*; bacterial vaginosis; trichomoniasis; diabetic foot infections; fistulizing Crohn's disease (may help drainage). ? Chronic use may have benefit in Crohn's, but risk of AE.[5] • **AE**: **GI upset**, metallic taste, headache, vaginitis, peripheral/optic neuropathy (long-term use). **Rare**: neurotoxicity, leukopenia, skin reactions (rash, pruritus, SJS/TEN). • **CI**: Use of disulfiram in previous 2 weeks; alcohol during and 3 days after therapy. • **DI**: disulfiram-like reaction with alcohol; ↑INR and bleeding risk with warfarin; ↑SJS risk with mebendazole. • **M**: neuropathy if long-term use (e.g. > 6 wks); CBC.	**Peds**: 15-**30**-50mg/kg/day po divided q8h **Adult**: 250-500mg po q8-12h **Max**: 4000mg/day Drug of choice in mild-to-moderate (i.e. WBC<15 & SCr<1.5x baseline) initial or first-recurrence *C. diff* infections. Dose = 500mg TID po x 10-14 days.	$12 $12-33 $72
Nitrofurantoin MACROBID MACRODANTIN, g **Dosed q6h:** 50mg macrocrystal capsule; 50, 100mg tab $P_{1,2}$ P_3 L **Dosed q12h:** 100mg macrocrystal capsule MACROBID	• Damages bacterial DNA/proteins (bacteria convert nitrofurantoin into reactive forms). Multiple sites of attack → resistance slow to develop. **Coverage**: *Staphylococci*; *E. coli*; *Enterococcus faecalis*; *Citrobacter*; *Klebsiella*. • **Useful in**: First-line therapy in UTIs (only 5 days needed if uncomplicated). Avoid if suspected pyelonephritis. • **AE**: Common: darkens urine, nausea, headache. Very rare: SJS/TEN → 7 per 100,000 patients;[6] acute hepatic reactions. Long-term use: neuropathy, pulmonary fibrosis, hepatic fibrosis. • **CI**: CrCl <30mL/min; pregnancy at term (36-42 wks gestation, risk of hemolysis); G6PD deficiency (risk of hemolysis). • **DI**: Few. May ↑ hyperkalemic effect of spironolactone; may ↓ effect of norfloxacin. • **M**: signs of pulmonary toxicity; signs of numbness or tingling of the extremities; CBC, LFTs, SCr if chronic use. • Heavily concentrates in urine (>100x serum level if healthy kidneys). Minimal change to gut flora.	**Peds**: 5-7mg/kg/day po divided q6h **Adult**: 100mg MACROBID po q12h **with food** **Max**: 200-400mg/day Increased absorption when taken with food See **Online Extras** 💻 for instructions on compounding a pediatric suspension, or round to nearest ¼ tab	$18 $27 $27-43
Fosfomycin MONUROL 3000mg powder sachet ☎ ✆ For UTI, NOT pyelonephritis. P L	• Inhibits cell-wall formation. Bactericidal. **Coverage**: ?*Staphylococci*; *Enterococci*; *Enterobacteriaceae*. Often coverage even if multi-drug resistance (MRSA, ESBL-producing organisms, VRE). • **Useful in**: UTIs. Avoid if suspected pyelonephritis. Safe in pregnancy but usually better options. • **AE**: GI upset, diarrhea, headache, hypokalemia. Significant adverse effects rare with short-course use. • **DI**: Usually no significant drug interactions.	**Peds**: 2000mg x 1 dose **Adult**: 3000mg x 1 dose **on empty stomach** **Max**: 3000mg x 1 dose	$38 $38 $38
Linezolid ZYVOXAM, g 600mg tab ☎ ✆ NIHB prior approval = treatment of: -proven VRE -proven MRSA with vancomycin intolerance Excellent bioavailability P L	• Inhibits bacterial protein synthesis. Usually bacteriostatic, but bactericidal against *Streptococci*. **Coverage**: *Streptococci*; *Enterococci* (including VRE); *Staphylococci* (including MRSA). • **Useful in**: multi-drug resistant infections (including pneumonia, skin and soft tissue, etc.). **Alternative to vancomycin** (e.g. MRSA with vancomycin intolerance; vancomycin-resistant *Enterococci*). • **AE**: headache, N/V/D, rash, ↑LFTs. Rare (but more common if > 2wks therapy): reversible myelosuppression (e.g. ↓platelets, anemia, leukopenia); peripheral/optic neuropathy; lactic acidosis • **DI**: ↑serotonin syndrome risk with SSRIs, MAOIs, etc. Rifampin decreases levels. • **M**: CBC weekly; ophthalmic tests if >3mos therapy	**Peds**: 30mg/kg/day po divided q12h **Adult**: 600mg po q12h **Max**: 1200mg/day	$802 $802 $802
Probenecid BENURYL 500mg tab ✗ ⊗ Non-prescription → over the counter P L	• Prolongs penicillin levels by competitively inhibiting their excretion. Give 30-45min prior to IV penicillin dose. • Occasionally useful when IV therapy is needed in an outpatient setting to ↑convenience / ↓ home care visits (e.g. in syphilis to ↓ penicillin dosing to q24h IM; in cellulitis to ↓ IV cefazolin dosing to q24h).[23] • **AE**: flushing, rash, GI upset, dizziness, headache.	**Peds**: 40mg/kg/day divided q6h **Adult**: 500mg po QID 30-45 min prior to IV abx Alternate: 1-2g daily 30 min pre-cefazolin **Max**: 2000-3000mg/day	$19 $19 $19-23
Vancomycin VANCOCIN, g 125, 250mg cap ☎ ✆ See IDSA *Clostridium difficile* guidelines [2010] P L	• Inhibits cell-wall formation. **Coverage**: The only oral use is for treatment of *Clostridium difficile* colitis (drug of choice if severe infection, or if second recurrence of *C. diff* infection; taper over ~8wks in recurrent infections.) • **AE**: rare when used po. **DI**: Usually no significant drug interactions. **M**: Essentially no oral absorption (used po for local effect in bowel); however, dialysis patients may require a random vancomycin level if toxicity suspected.	**Peds**: 40mg/kg/day po divided q6h **Adult**: 125mg po q6h **Max**: 500mg po q6h if ↓BP, shock, ileus, megacolon {If severe complicated C. diff consider adding metronidazole 500mg IV q8h}	$234 $234 $856

Methenamine mandelate MANDELAMINE 500mg po q6h $33 ⊗ P L creates acidic urine; indicated for UTI prophylaxis, but not first line (limited evidence);[22] likely inefficacious in catheterized patients; **AE**: rash, GI upset, bladder irritation, ↑LFTs; **DI**: α-agonists, β-agonists, amphetamines, sulfonamides, acetazolamide, antacids; **M**: Urinalysis, periodic LFTs. **CI**: severe hepatic dysfunction, gout.

Useful Links: **Infectious Disease Society of America** www.idsociety.org/IDSA_Practice_Guidelines; **Sanford Guide to Antimicrobial Therapy** www.sanfordguide.com; **Bugs & Drugs** www.bugsanddrugs.ca **RxFiles** www.RxFiles.ca/abx

Saskatchewan Antibiograms: **Regina** 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*, others. ↓ **antibiotic-associated diarrhea**; separate >2hrs from antibiotics.[20] *S. boulardii* 1g daily for *C. difficile* diarrhea (caution: immunocompromised, pancreatitis).[21]

Rx Patient Name: _____ Date: _____

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**

RX FILES

Visit www.RxFiles.ca/ABX for more information.

We asked some clinicians: "How do you deal with patient expectations around antibiotics?"

PATIENT SAYS:		POSSIBLE CLINICIAN RESPONSE:	
I feel really rotten!	→	*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!*	Feeling really sick, sniffles, runny nose, cough... ≠ bacterial
I really think I need something.	→	*Yes, for sure. You need to stay home & rest for a day. Here is an information hand-out and a script with options for symptom management.*	An information hand-out + a "non-Rx" script-pad
But, last time I got antibiotics!	→	*In the past, we sometimes used antibiotics, they didn't work, but the practice has given us "superbugs"!*	Superbugs!
I drove and waited a long time. I don't want to have to come back!	→	*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.*	A "watch and wait" prescription option [ii]
I've been coughing for two weeks...	→	*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?*	Bronchitis & cough
I've been coughing steady, feverish, and feel like dying.	→	*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.*	CXR
I think I'd like an antibiotic just in case. Can't go wrong, right?	→	*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!*	Antibiotic harms: side effects & bacterial resistance

EVIDENCE AROUND REDUCING UNNECESSARY ANTIBIOTICS?

- Studies have demonstrated patient satisfaction with care for acute bronchitis depends most on physician-patient communication, not antibiotic treatment. [iii, iv]
- One study found that the duration of office visits for acute respiratory infection was only one minute longer when antibiotics were not prescribed. [v]
- A change in antibiotic reimbursement resulted in fewer antibiotics prescribed, and a reduction in the level of antimicrobial resistance. [vi]

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.

ADDITIONAL TIPS FOR GETTING PATIENT BUY-IN

- → Use the term "chest cold" or "viral upper respiratory tract infection" as this makes it easier to convince patients they do not need antibiotics.
- → Viruses commonly make you feel sick all over your body.
- → 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.
- → Fever is how our bodies fight off any infection and not an indication of a bacterial infection.
- → 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.
- → Most sore throats are viral infections. Strep throat can only be diagnosed by a throat swab.
- → 70-80% of ear infections get better without antibiotics.
- → Antibiotics do not reduce the duration of viral illness, but may cause harms (nausea, diarrhea, allergic reactions, etc.)
- → Always provide a) patient education, b) symptom duration, and c) when to return.
- → Hand washing!! Important for sick contact prevention.

TYPICAL SYMPTOM DURATION FOR SELECT VIRAL ILLNESS

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

Patient Pages, Tools, Links: 1) Why didn't I get antibiotics today: http://generations.ourmd.ca/Doctor/secem-att-store.nsf/fa/GFLK-A9WP9V/$FILE/No-Antibiotics.pdf ; 2) ABX Public/Patient Resources & Links: www.RxFiles.ca/ABX; For more information & references, see www.RxFiles.ca