Antibiotics & Common Infections

ABX-2: Uncomplicated Cystitis & Skin

Stewardship, Effectiveness, Safety & Clinical Pearls- April 2017

ABX-2 RELATED LINKS

CANADIAN GUIDELINES/REFERENCES

Bugs & Drugs:
http://www.bugsanddrugs.ca/

MUMS Guidelines:
http://www.mumshealth.com

CYSTITIS / UTI

U.S. IDSA 2010:
Acute Uncomplicated Cystitis and Pylonephritis (UTI)
https://academic.oup.com/cid/article-lookup/52/5/e103

SK MOH 2013:
UTI in Continuing Care Settings
https://saskpic.ipac-canada.org/photos/custom/UTI%20Guidelines%2019April2013.pdf

SOGC 2010:
Recurrent UTI
http://www.jogc.com/article/S1701-2163(16)34717-X/pdf

CUA 2011:
Recurrent UTI
https://www.cua.org/themes/web/assets/files/guidelines/en/1121.pdf

SKIN & SOFT TISSUE INFECTIONS

U.S. IDSA 2014:
Skin & Soft Tissue Infections
https://academic.oup.com/cid/article-lookup/59/2/e10

EXTRAS FROM RxFILES

Geri-RxFiles UTI in Older Adults:
http://www.rxfiles.ca/rxfiles/uploads/documents/GeriRxFiles-UTI.pdf

Nitrofurantion Q&As/Extras:
- Evidence/Safety, rare toxicity

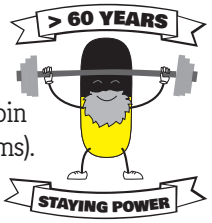
SSTI Related Trial Summaries:
- Clindamycin vs TMP/SMX
- Skin Abscess: I&D +/- ABX

RxFILES ACADEMIC DETAILING ON ABX

We are excited to bring out the ABX-2 topic on the treatment of uncomplicated cystitis and skin & soft tissue (SSTI) infections. The new charts in this newsletter will support our spring academic detailing discussions with providers in Saskatchewan. Our discussions on ABX-1 were very well received and we know many of you made use of the extra support tools such as the "Gone Viral?" office/clinic posters and the patient friendly "Viral Prescription Pad". These are all available at www.RxFiles.ca/abx.

ABX-2: A FEW PEARLS FROM INSIDE THAT CAUGHT OUR EYE...

UNCOMPLICATED CYSTISIS - Page 2 - 3



1) **Staying Power: > 60 years & still 96% or better!**
Susceptibility of *E. coli*, the most common urinary pathogen, to nitrofurantoin (MACROBID) remains at 96% or better in Saskatchewan (per recent antibiograms).

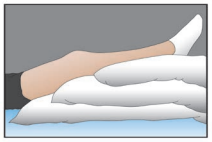
2) **60% - Are you kidding?!**
In some institutional settings, like long-term care, *E. coli* resistance to ciprofloxacin can be as high as ~60%. No wonder antimicrobial stewardship messaging suggests "Reserve to Preserve" for when we really need it!

3) **Urine cultures are not required - for most symptomatic acute uncomplicated cystitis.**
Empiric antibiotic Rx is suitable based on patient **symptoms (e.g. dysuria, frequency) & history.**

SKIN and SOFT TISSUE INFECTIONS - Page 4 - 8

4) **Incision and Drainage (I&D) - key to successful treatment of skin abscess.**
ABX just don't penetrate abscesses very well. I&D alone results in cure >80% of the time.

5) **Elevation of the affected limb, e.g. above level of the heart - often essential in the successful treatment of cellulitis.**



6) **My name is clindamycin - I usually play 3rd line.**
For most SSTI, resistance to clindamycin, and safety are major concerns. There are usually better options.

BETA LACTAM ALLERGY and ANTIBIOTIC HARMS - Page 9 - 10

7) If you test 1000 patients with penicillin "allergy", only ___ will have a true IgE mediated allergy (e.g. anaphylaxis).
Know your options! (see pg 9)

PEARLS for the MANAGEMENT of UNCOMPLICATED Cystitis in Women:

- **Urine culture** is not required for most acute, uncomplicated cystitis and asymptomatic bacteriuria ("Symptom-Free Pee, Let It Be") {see also Geri-RxFiles}.
- **Consider nitrofurantoin as empiric drug of choice** except if CrCl <30 mL/min.
- Consider TMP/SMX as a suitable alternative to nitrofurantoin in those with low risk of resistant bacteria (e.g. no history of UTI or antibiotic use in the past 3-6 months).
- If bacteria is resistant to nitrofurantoin and TMP/SMX, consider fosfomycin.
- **"Test of cure" is not recommended** following treatment if patient asymptomatic.
- Prior to initiating prophylactic antibiotics in recurrent cystitis, encourage sexually active women to **avoid spermicide** & consider an alternative form of contraception.

Pre-Treatment Consideration

⇨ Urine culture is rarely required in women if uncomplicated & only local symptoms!

- Symptoms (e.g. dysuria & frequency) associated with high probability of cystitis.[4]

⇨ Urine culture is typically required in the following patients:

- Recent (e.g. <3-6 month) hospitalization or travel outside Canada/USA
- Early recurrence of cystitis (i.e. less than ~ 1 month)
- Previous non-*Escherichia coli* gram negative organism or previous ESBL cystitis
- Complicated UTI {see Table 1}, pyelonephritis suspected, or pregnancy

Table 1: Factors that Would Classify a UTI as "Complicated"* [5,6]

Anatomic abnormality	Cystocele, diverticulum, fistula
Iatrogenic	Indwelling catheter (catheter removal often curative!)
Voiding dysfunction	Vesicoureteric reflux, neurologic disease
Urinary tract obstruction	Bladder outlet obstruction, ureteral stricture, ureteropelvic junction obstruction, urolithiasis

* may sometimes be considered as complicated: surgery, incontinence, pregnancy, diabetes (especially if long-term complications i.e. neuropathy), male, immunosuppression.

⇨ Urine culture is NOT indicated in most asymptomatic patients, as there is no benefit and potential harm (e.g. ↑ resistant bacteria) with antibiotic treatment. (Exceptions: pregnancy or those awaiting urinary surgery/manipulation). [7,8]

Most Common Pathogen & Susceptibility Concerns (Outpatient/Community)[9-10]

- *Escherichia coli* non-ESBL is the most common pathogen (75-95% of cystitis cases).
  - Susceptibility to nitrofurantoin in SK: **96%** Regina[2016], **96%** Saskatoon[2015]
  - Susceptibility to TMP/SMX in SK: 76% Regina[2016], 77% Saskatoon[2015]
  - Susceptibility to ciprofloxacin in SK: 83% Regina[2016], 85% Saskatoon[2015]
    {Note: susceptibility to ciprofloxacin is much lower in LTC (55% Regina, 40% Saskatoon)}
- A local resistance of >20% for TMP/SMX often serves as an arbitrary cut off for empiric antibiotic choice.[5 IDSA'10] However, if first cystitis episode, susceptibility likely better than it appears in the antibiogram, where patients with more complicated & recurrent UTIs may be over-represented.
- Less common pathogens: other *Enterobacteriaceae* organisms (e.g. *Klebsiella* species, *Proteus mirabilis*), *Staphylococcus saprophyticus*…

Treatment Approach For Acute, UNCOMPLICATED Cystitis in Women

- Nitrofurantoin is a good empiric first choice as it has retained excellent susceptibility (**96%** Outpatient Regina, Saskatoon) to *Escherichia coli* despite ~65 years of use {see Table 2}.
- In SK, TMP/SMX is a suitable alternative in those with uncomplicated, 1st episode cystitis and without UTI or antibiotic use in the past 3-6 months {see Table 3}.

Table 2: Empiric Drug Regimen(s) of Choice {see also RxFiles Antibiotic Comparison-Expanded chart[A]}

MACROBID	100mg po BID	x5 d $19	- avoid if CrCl **<30mL**/min[11] - short-term treatment well tolerated (esp macro formulations) and SAEs are rare (caution/discontinue if symptoms)
MACRODANTIN, g	50-100mg po QID	x5 d $20-29	
Nitrofurantoin, g	50-100mg po QID	x5 d $14-16	

Table 3: Alternative Regimens

TMP/SMX BACTRIM, SEPTRA, Cotrimoxazole, g *	1 DS tab po BID {1DS tab=160/800mg}	x3 d $11	- option depending on local resistance & if recent history of UTI/antibiotics - 1 SS tab BID if CrCl 15-30mL/min
Trimethoprim, g *	200mg po daily	x3 d $12	- monotherapy option if sulfa allergy - alternate dosing: 100mg po BID
Cephalexin KEFLEX, g	250mg po QID	x7 d $17	- only if susceptible on C&S results - requires QID; may be less effective
Fosfomycin MONUROL	3g po given	x1 dose $38 ☎ ✆	- reserve for allergy, resistance, or CI to MACROBID & TMP/SMX; po option for urinary ESBLs & *Pseudomonas*
Suspension (powder sachet; dissolve in ½ cup water); single dose			
Amoxicillin/clavulanate CLAVULIN, g	875/125mg po BID	x7 d $19	- reserve for more severe infections (e.g. pyelonephritis) or when other options lacking (e.g., allergy, high probability/documented resistance) - extensive fluoroquinolone use associated with ↑Gm –ve resistance
Ciprofloxacin CIPRO, g	250mg po BID **	x3 d $15 ☎ ▼	
Norfloxacin, g 400mg po BID x 3 d $14 ☎ ▼ is a suitable alternative to ciprofloxacin.			

* Caution: potential ↑ K +drug interactions **Higher doses of ciprofloxacin used if pyelonephritis (i.e., 500 mg po BID)
{Note: fosfomycin, nitrofurantoin, norfloxacin & moxifloxacin – should not be used if pyelonephritis is suspected!}

- No role for follow-up culture ("test of cure") if patient asymptomatic.[12 Choosing Wisely]

Treatment Evidence Summary

Antibiotics are recommended for symptomatic cystitis. In 2 RCTS (n=884, n=78), placebo was associated with prolonged symptoms & a small risk of progression to pyelonephritis (0.4-2.6%, NS vs antibiotic), but also resulted in clinical cure 25-42% of the time.[13,14] With antibiotics, symptom relief may be expected within 36-48 hours.

Nitrofurantoin x5-7 days has similar effectiveness to alternative regimens. In RCTs, there was no difference in clinical cure rates vs TMP/SMX x3-7 days, ciprofloxacin x3 days, & fosfomycin x1 dose.[15-17] Nitrofurantoin x3 days is not recommended as this regimen resulted in less clinical/bacterial cure than TMP/SMX x3 days (NNH=5).[18]

Short courses of nitrofurantoin are well tolerated (however, urine color often darkens). SAEs (e.g. pulmonary toxicity, peripheral neuropathy, hepatic, & hemolytic) are rare with short term therapy (≤14 days).[19] With prophylactic therapy, 2 meta-analyses of controlled trials (N=12, n=1063; N=17, n=511) have reported 2 cases of pulmonary toxicity.[20,21] Surveillance data have reported SAEs in less than 0.003% of nitrofurantoin courses.[22] 💻 {see Online Extras for Nitrofurantoin Q&As}

💻=online extras =↓dose for renal dysfx ☎=Exception Drug Status Sk ▼=covered NIHB ✆=prior approval NIHB **aHR**=adjusted hazard ratio **AE**=adverse events **CI**=contraindication **CrCl**=creatinine clearance **C&S**=culture & sensitivity **CUA**=Canadian Urological Association **DS**=double strength **d**=day(s) **DS**=double strength (1DS tab= 160/800mg) **eGFR**=estimated glomerular filtration rate **ESBL**=extended spectrum beta-lactamases (highly resistant Gram-negative bacteria) **g**=generic drug available **Gm –ve**= gram negative **HS**=bedtime **IDSA**=Infectious Diseases Society of America **LTC**=long-term care **N** or **n**=number **NNH**= number needed to harm **NNT**=number needed to treat **NS**=non-statistically significant **OR**=odds ratio **RCT**=randomized controlled trial **SAE**=serious advere events **SK**=Saskatchewan **SOGC**=Society of obstetricians and Gynaecologists of Canada **SS**=single strength (1SS tab=80/400mg) **TMP/SMX**=trimethoprim/sulfamethoxazole **UTI**=urinary tract infection

CLINICAL Q&A

Nitrofurantoin: Is nitrofurantoin suitable for those with reduced renal function?

- In adults ≥65 years, nitrofurantoin recommendations were revised from CrCl ≥60 mL/min[Beers 2012] to now recommend use in patients with CrCl of ≥30mL/min[Beers 2015 Low Quality Evidence, Strong Recommendation 11]. Two retrospective studies (n=21,317[23], n=356[24]) were conducted using the Modified Cockcroft-Gault (MCG), Elderly-Adjusted MCG, and/or Modification of Diet in Renal Disease (MDRD) equations to calculate renal function. There was no difference in clinical cure; however, 1 study demonstrated greater SAE (e.g., pulmonary reactions leading to hospitalization) in those with eGFR <50 mL/min/1.73m^2 vs eGFR ≥ 50 mL/min/1.73m^2 (aHR 4.13, 95% CI 1.31-13.09).[23] Studies are limited by the number of patients included with renal function <50 mL/min {n=187/21,317 (0.9%)[23], n=72-193/356 (20-54%) depending on equation[24]}.

Fosfomycin: What is its role in uncomplicated cystitis?[25-28]

- Low rate of resistance seen, even for ESBLs and *Pseudomonas* species. However, resistance concerns have arisen in some countries (e.g. Spain) with more extensive use. Thus, reserve in order to preserve activity for more resistant cases.
- Reasonable to consider use when nitrofurantoin & TMP/SMX are not an option.

Trimethoprim (TMP): Does trimethoprim have same resistance pattern as TMP/SMX?

- If a bacteria is resistant to TMP/SMX, it would also be resistant to TMP alone.
- When SMX is CI (e.g. sulfa allergy, pregnancy 3rd trimester), TMP monotherapy may be used. European experience suggests similar resistance patterns and clinical effectiveness to TMP/SMX.[29-33]

Which "complicated" patients may be appropriate for "short course" therapy?

- Healthy, community-dwelling post-menopausal women, people with diabetes & no long-term complications (e.g. neuropathy), & pregnant woman with cystitis may be successfully treated with "short-course" therapy.[8,34-37]

CYSTITIS: MANAGING RECURRENCE[6,38]

Definitions

- **Relapse**: Original organism re-presents within 2 weeks of completing therapy.
- **Reinfection**: Different organism (generally) presents after 2 weeks of therapy.
- **Recurrence**: Defined as at least 2 uncomplicated, culture-positive UTIs in 6 months or at least 3 in 12 months. Recurrence may sometimes be related to an anatomical cause (incomplete bladder emptying, bladder cancer, etc.) & warrant further investigation.

How does acute treatment change in recurrent infections?

- If recurrence occurs within ~30 days, obtain a urine culture, and rule out pyelonephritis. Consider using a different empiric antibiotic than previous, as presence of resistant bacteria is more likely. If previous 3 day course, may treat for 7.
- If recurrence occurs after ~30 days, a urine culture is likely not necessary. It is reasonable to use the same 1st line empiric antibiotic, as with the initial cystitis episode, if patient previously responded.

What is the evidence for treatment options in those with frequent recurrence?

a) Lifestyle modification & herbal strategies

- In a case-control study (n=482), spermicide use was associated with increased UTIs (OR 1.8). Post-coital voiding & increased fluid intake were not associated with less UTIs.[39] Encourage sexually active women to avoid spermicide use & consider an alternative form of contraception.[6 CUA'11 (4,C), 38 SOGC'10 (II,2B)]
- In a meta-analysis (N=4 RCTs, n=594) cranberry juice/tablets did not reduce UTIs vs placebo in women with recurrent UTIs.[40] Additionally, probiotics did not reduce UTIs compared to placebo in a meta-analysis (N=4, n=275), but data is limited.[41]

b) Antimicrobial prophylaxis – oral regimens {see also Table 4}

- Antibiotics are effective for UTI prophylaxis (NNT=2) but result in more AEs (NNH=14).[42] No antibiotic was superior; consider safety, cost, & local resistance.[43]

c) Topical estrogen prophylaxis {see also RxFiles 11 Ed, Menopause chart}

- This is an option in post-menopausal women.[SOGC'10 (1,A), CUA'11 (1,A)] Creams, vaginal tablets and the vaginal ring have all been studied and are reasonable options.[44]

Table 4: Oral Regimens – Recurrent Cystitis Therapy
(defined as ≥2 uncomplicated, culture positive UTIs in 6 months or ≥3 in 12 months)

Acute self-treatment	⇨ Consider in patients able to recognize symptoms. Prescribe to have on hand at home for first onset of symptoms.	
Nitrofurantoin * MACROBID	100mg po BID x5 days	- high concordance between self-diagnosis & culture in appropriately selected patients[45] - advise patients to **contact provider if symptoms do not resolve/improve** within 48 hours despite therapy
TMP/SMX	1 DS tab (160/800mg) po BID x3 days	
TMP	200mg po daily x3 days	
Ciprofloxacin ** ☎▼	250mg po BID x3 days	
Post-coital Prophylaxis	⇨ Consider in patients when cystitis routinely presents within 24-48 hours of intercourse.	
TMP/SMX	½ SS tab (40/200mg) po x1	- post-coital approaches (i.e. **single dose** taken **within 2 hours** of intercourse) result in less antibiotic use than continuous approaches
TMP	100mg po x1	
Nitrofurantoin *	50-100mg po x1	
Cephalexin ***	250mg po x1	
Ciprofloxacin **☎▼	125mg po x1	
Norfloxacin ** ☎▼	200mg po x1	
Continuous Prophylaxis	⇨ Option; however, increased concern for AE & impact on bacterial resistance. Consider stopping in 6-12 months.	
TMP/SMX	½ SS tab (40/200mg) po HS [$11/30days]	- TMP/SMX alternate dosing: 1 SS (80/400mg) 3 x weekly [$11/30days] - if patient becomes symptomatic, obtain urine culture and treat accordingly
TMP	100mg po HS [$19/30days]	
Cephalexin ***	125-250mg po HS [$14-18/30days]	
Nitrofurantoin *	50-100mg po HS [Nitrofurantoin $17-18/30days, MACROBID $36/30days, MACRODANTIN $25-38/30days]	

Prophylaxis: initiate after UTI eradication (confirm with a negative culture 1-2 wks post-treatment).[38 SOGC'10 (III,L)]
*If choosing nitrofurantoin, either Nitrofurantoin/MACRODANTIN, g 50-100mg or MACROBID 100mg are reasonable. Beers 2015 recommends avoiding long-term use of nitrofurantoin in those ≥65 years due to adverse effects (e.g. pneumonitis, peripheral neuropathy).[11 Low Quality Evidence, Strong Recommendation] {see Nitrofurantoin Q&As[B]}.
** Reserve fluoroquinolones due to resistance concerns & serious rare AE (eg. on tendons, muscles, nerves/CNS). The FDA generally considers **risk to be greater** than the benefits if used for uncomplicated UTI.
***Strength of cephalexin may require splitting the non-scored 250mg tablet (e.g. pill-cutter).

PEARLS for the MANAGEMENT of SSTI Treatment & Antibiotic Stewardship

- **Incision & drainage** (I&D) is key to successful treatment of purulent skin infections!
  - incision & drainage alone (i.e. without antibiotics) is often sufficient for clinical cure
- **Avoid long durations** of antibiotic treatment (e.g. >10days); 5 days is often adequate.
  - Resolution of skin inflammation takes time & continues after antibiotic stopped
- **Elevation of an affected limb** is usually essential for successful cellulitis therapy.
- Before treating, consider type of infection, risk for *Staph,* & if CA-MRSA is likely.
- Consider **TMP/SMX or doxycycline** over clindamycin for **CA-MRSA**, due to local resistance concerns & adverse events associated with clindamycin.
- Topical antibiotics are as effective as oral antibiotics for limited & localized impetigo.

OVERVIEW & PRE-TREATMENT CONSIDERATIONS

SSTI*

Assess for red flags (see footnote)

Non-Purulent	Purulent (e.g. Pus)
e.g. non-bullous impetigo, non-purulent cellulitis	e.g. bullous impetigo, carbuncles, cutaneous abscess, folliculitis, furunculosis, purulent cellulitis
Simple skin infections, including cellulitis, are Gram-positive infections!	
Think predominantly *Strep*!	**Think predominantly *Staph*!**
Culture usually **not** required as not informative in guiding therapy. Empirically cover for ***Group A Strep***. (GAS) Antibiotic required. (Topical suitable for some localized & superficial SSTI)	**Incision & Drainage (I&D)** I&D cornerstone of treatment as antibiotics poorly penetrate pus. Consider swabbing the drainage/exudate on all moderate to severe infections on the initial visit, especially if potential MRSA. However, avoid initiating antibiotics based on the C&S if the infection is improving. I&D alone often adequate. May add antibiotics if ↑ risk (e.g. abscess >5cm, systemic symptoms, extensive surrounding cellulitis).
	Low risk for CA-MRSA / **High risk for CA-MRSA**
Treatment should empirically cover GAS e.g. **cephalexin** Consider topical antibiotics for limited & localized impetigo, e.g. **mupirocin** BACTROBAN	Treatment should empirically cover for MSSA e.g. **cephalexin** or **cloxacillin**. / Treatment should empirically cover for CA-MRSA e.g. **TMP/SMX** or **doxycycline**
see page 5 for impetigo & page 6 for non-purulent cellulitis	**see page 5 for impetigo, folliculitis, furunculosis, carbuncles & abscess, & page 6 for purulent cellulitis**

* **Red Flags** for rapidly progressive SSTI requiring other assessment/treatment considerations: any rapid deterioration, sign of septicemia, shock or confusion, immunosuppressed patient, recent trauma or surgery, liver disease, anaesthesia of involved area, systemic symptoms or pain out of proportion to local findings, animal & human bites (punctured or closed wound), progression despite antibiotic use.

IDSA 2014 divides SSTI into non-purulent vs purulent for treatment approach.

MOST COMMON SSTI PATHOGENS & SUSCEPTIBILITY CONCERNS

Group A *Streptococcus*, or "GAS"

⇨ Likely if non-bullous impetigo, cellulitis without pus/lymphangitis

***Staphylococcus aureus*:**

⇨ in purulent SSTIs, bullous impetigo, folliculitis, boils, abscesses, wound infection

- **MSSA**: methicillin-sensitive *Staph. aureus* (i.e. sensitive to cloxacillin in Canada)
- **MRSA**: methicillin-resistant *Staph. aureus* (not susceptible to β-lactam antibiotics)
  - in SHR & RQHR, approximately ⅓ of isolates are MRSA
- **CA-MRSA**: community associated MRSA
  - onset in community & without health-care associated risk factors
  - in SHR & RQHR, good susceptibility (≥92%) to doxycycline or TMP/SMX; less susceptibility to clindamycin for MRSA (50-88%)
- **HCA-MRSA**: health care associated MRSA

When is it necessary to cover for CA-MRSA if suspecting a *Staphylococcal* cause?

- Coverage for CA-MRSA may be recommended if:
  - patient is from a highly endemic region for CA-MRSA
  - CA-MRSA risk factors are present (see Table 1)
  - clinical judgement warrants (e.g. patient follow-up unreliable, immunocompromised, seriousness of infection, etc.)
  - lack of improvement on a beta-lactam or systemic symptoms

Risk factors for CA-MRSA

The CDC **5 C's**: ***crowding***, frequent skin ***contact***, ***compromised*** skin, sharing ***contaminated*** personal items, & lack of ***cleanliness***.

- Age: <2 years old & >65 years old
- Athletes (mainly contact sports)
- Men who have sex with men
- Persons living in correctional facilities
- History of colonization or recent infection with CA-MRSA
- Antibiotic use in the past 6 months
- Recent invasive procedures e.g. dialysis
- IV drug use
- Military personnel
- Homeless persons
- Prior hospitalization for SSTI (check MRSA screen from hospital if available)
- Trauma associated

- Of note, SSTIs often respond to therapy that does not cover CA-MRSA, even if CA-MRSA is endemic or cultured. Empiric CA-MRSA coverage may not be essential.
- There are no reliable signs/symptoms to distinguish CA-MRSA from other purulent SSTIs.
- Swab purulent drainage / exudate on the initial visit if MRSA is suspected.

Is there a role for over-the-counter topical antibiotics in treating impetigo?

- Reserve topical antibiotics for infections (e.g. impetigo). Overuse for non-infectious conditions (e.g. rash) has led to resistance with these agents.
- There is limited evidence that bacitracin, gramicidin, neomycin &/or polymyxin B (either as single agents or various combinations) can be used for impetigo.
- These OTC topical antibiotics were less effective than mupirocin BACTROBAN & fusidic acid FUCIDIN, when pathogens were sensitive to these agents.
- Unpublished in vitro Saskatchewan data suggests **POLYSPORIN TRIPLE OINTMENT**, g ✗▼ (bacitracin, gramicidin, polymyxin B; $15-$20) can be considered in areas with local resistance concerns to mupirocin or fusidic acid.

IMPETIGO

MOST COMMON PATHOGENS:

- **Non-bullous** ("honey-crusted", 70% of cases): Group A *Streptococcus* *Staphylococcus aureus* (usually MSSA)
- **Bullous** (30% of cases): *Staphylococcus aureus* (usually MSSA)

EMPIRIC DRUG REGIMEN OF CHOICE:

- A **topical antibiotic** is preferred if the infection is limited & localized (i.e. 2-3 small areas). Crusts do not need to be removed prior to applying.
- An **oral antibiotic** is preferred if the infection is unresponsive to topical antibiotics (i.e. no improvement after 24-48 hours), recurrent or widespread (i.e. numerous or large lesions), or during an outbreak; or if the patient has constitutional symptoms suggesting bacteremia, a fever, lymphadenopathy, valvular heart disease, is immunocompromised, or <1 month old.
- **Duration of therapy** is generally 5 to 7 days.

	PEDIATRIC DOSING	ADULT DOSING
TOPICAL ANTIBIOTICS preferred if limited & localized infection		
Mupirocin 2% ointment or cream BACTROBAN, g $22	Apply sparingly to lesions TID	
Fusidic acid 2% ointment or cream FUCIDIN $34	Apply sparingly to lesions TID to QID	
ORAL ANTIBIOTICS see above for when oral preferred over topical		
Cephalexin	50-100mg/kg/day PO ÷ QID	500mg PO QID
Cloxacillin	50mg/kg/day PO ÷ QID	500mg PO QID
PENICILLIN ALLERGY: TYPE I HYPERSENSITIVITY (i.e. anaphylaxis)		
Erythromycin*¶	30-40mg/kg/day PO ÷ QID	250-500mg PO QID
Clindamycin ¶	15mg/kg/day PO ÷ TID-QID	300-450mg PO TID

*Erythromycin is the most studied macrolide, but azithromycin or clarithromycin may also be used
¶ Monitor clinical response due to potential resistance concerns

- If a swab was done & the culture only shows *Streptococcus*:
  - **penicillin V** 25,000-90,000 units/kg PO ÷ QID or 300-600mg PO QID

IMPETIGO DUE TO MRSA (less common):

- **Topical antibiotics**: consider mupirocin if no local resistance concerns
- **Oral antibiotics:** consider TMP/SMX or doxycycline (see page 6 for dosing)
  - will cover MRSA but has poor/no coverage of Group A *Streptococcus*

TREATMENT EVIDENCE FOR CLINICAL CURE:

Based on a 2012 Cochrane Review of 68 RCTs with N=5,578:

- Topical mupirocin & fusidic acid had similar efficacy (4 RCTs, n=440; RR 1.03, 95% CI 0.95-1.11).
- Topical mupirocin or fusidic acid were **equally effective** as oral antibiotics (22 RCTs, n=884); however, studies are lacking in those with more extensive impetigo.
  - topical mupirocin was slightly superior to oral erythromycin (10 RCTs, n=581; RR 1.07, 95% CI 1.01-1.13)
- Combining a topical & oral antibiotic **failed to show additional benefit** over a topical antibiotic alone (1 RCT, n=49).

FOLLICULITIS/FURUNCULOSIS/CARBUNCLE

MOST COMMON PATHOGENS: *Staphylococcus aureus* (usually MSSA)

TREATMENT APPROACH – FOLLICULITIS / FURUNCULOSIS:

- If limited involvement or small pustule size (1-2mm): usually self-limiting; hot compresses & anti-septic cleanser may be beneficial (e.g. chlorhexidine)
- If extensive infection or above ineffective: topical antibiotic
  - mupirocin 2% ointment or cream BACTROBAN, g TID x 7 days
  - fusidic acid 2% ointment or cream FUCIDIN TID to QID x 7 days

TREATMENT APPROACH – CARBUNCLE: see purulent cellulitis (page 6) for antibiotics

- Incision & drainage (I&D), hot compresses & anti-septic cleanser (e.g. chlorhexidine)
- Consider systemic antibiotics in addition to I&D if: large (diameter ≥5cm) &/or multiple abscesses, extensive surrounding cellulitis, located in area difficult to drain (e.g. face, groin), constitutional symptoms or fever, debilitated elderly, immunocompromised, diabetic, or active cancer.

Note: "**Hot tub" folliculitis** caused by *Pseudomonas aeruginosa* will typically self-resolve in 7-10 days in immunocompetent patients. Hot tub or whirlpool should be cleaned.

ABSCESS, CUTANEOUS

MOST COMMON PATHOGENS: *Staphylococcus aureus* (usually MSSA) rarely *Streptococcus*, anaerobes, or polymicrobial

TREATMENT APPROACH:

- **Incision & drainage** (I&D):
  - for simple abscess (<5cm), I&D alone is often adequate IDSA 2014
  - From ***Choosing Wisely Canada***: Antibiotics usually do not help simple abscesses heal faster. Usually, draining a simple abscess is enough to heal the infection. In most cases, giving antibiotics does not help heal the infection any faster than just draining the abscess.
- **Antibiotic therapy** generally only indicated if: see purulent cellulitis (page 6) for treatment options
  - large abscesses (>5cm), extensive cellulitis, unresolving SSTI or rapid progression
  - abscess in area where I&D is difficult (e.g. face, hands, genitalia)
  - systemic illness symptoms e.g. ↑ temperature, respiratory rate, heart rate, WBC
  - significant comorbidities, immunosuppression, very young or very old

TREATMENT EVIDENCE: I&D ± ANTIBIOTICS in UNCOMPLICATED SKIN ABSCESSES

- A meta-analysis of 4 RCTs with N=589 patients found no difference in clinical cure rates when I&D + antibiotics was compared to I&D alone. Antibiotics provided a non-statistically significant reduction in recurrence.
- A recent RCT with N=1,265 patients who underwent I&D ± TMP/SMX 2 DS tablets BID x 7 days, found the addition of antibiotics resulted in:
  - a modest improvement in clinical cure (NNT=14, TMP/SMX 80.5% vs placebo 73.6%, 95% CI 2.1-11.7)
  - a similar NNH for gastrointestinal adverse events (NNH=15,TMP/SMX 42.7% vs placebo 36.1%, note: p-value & CI not provided)
  - no difference in the rate of invasive infections

NON-PURULENT CELLULITIS

- Cellulitis with no purulent drainage, exudates, or abscess

MOST COMMON PATHOGENS: Group A *Streptococcus*

- *Staph aureus* is less common (of which, ~⅔ of isolates in SHR & RQHR are MSSA)

TREATMENT APPROACH FOR NON-PURULENT CELLULITIS

- **Elevation of an affected limb** is usually essential for successful therapy

	Pediatric Dose	Usual Adult Dose	Comments
EMPIRIC THERAPY FOR *Group A Streptococcus* (GAS)			
Cephalexin	50-100mg/kg/day PO ÷ QID	500mg PO QID	- **100%** of **GAS** isolates in SHR [2015] & RQHR [2016] were sensitive to cephalexin - β-lactams do not cover **MRSA** - **penicillin allergy:** may still use if type IV rxn e.g. rash
EMPIRIC THERAPY FOR *Group A Streptococcus* (GAS) & MRSA Consider CA-MRSA for those who do not respond to β-lactams or with systemic toxicity.			
Cephalexin (or penicillin) **AND** [**TMP/SMX** BACTRIM, SEPTRA **OR** **Doxycycline**]	50-100mg/kg/day PO ÷ QID **AND** 8-12mg/kg/day (TMP) PO ÷ BID if >1 month old **OR** ≥9 years: 4mg/kg/day PO ÷ BID	500mg PO QID **AND** 1-2 DS tab PO BID **OR** 100mg PO BID	2 antibiotics because: - cephalexin covers **GAS**, but not **MRSA** - TMP/SMX & doxycycline have poor coverage for **GAS**, but cover **MRSA** (active against **92-100%** of **MRSA** isolates in SHR [2015] & RQHR [2016])
PENICILLIN ALLERGY: TYPE I HYPERSENSITIVITY (i.e. anaphylaxis) Avoid the below as empiric therapy, unless true penicillin allergy. Monitor response due to resistance rates.			
Clindamycin inducible resistance	20-40mg/kg/day PO ÷ TID to QID	300mg PO QID or 450mg PO TID	**RESISTANCE to clindamycin:** - **In SHR [2015]:** ▪ ~**25%** of **GAS** isolates ▪ **27%** peds, **50%** LTC, **37%** adults of **MRSA** isolates - **In RQHR [2016]:** ▪ ~**12%** of **GAS** isolates ▪ **12%** peds, **25%** adults & **43%** LTC of **MRSA** isolates
Erythromycin	30-40mg/kg/day PO ÷ BID	250mg PO QID or 500mg PO BID	**RESISTANCE to erythromycin:** - **In SHR [2015]:** ▪ **25%** of **GAS** isolates ▪ **35-60%** of **MRSA** isolates - **In RQHR [2016]:** ▪ ~**10%** of **GAS** isolates ▪ **48-90%** of **MRSA** isolates

See following page for additional information on the TMP/SMX dose.

PURULENT CELLULITIS ± ABSCESS

- Cellulitis with purulent drainage or exudates in the absence of a drainable abscess

MOST COMMON PATHOGENS: *Staphylococcus aureus*

- in SHR & RQHR, ~⅔ of isolates are MSSA; see page 4 for when to consider MRSA
- empiric coverage for Group A *Streptococcus* is unnecessary

TREATMENT APPROACH FOR PURULENT CELLULITIS

- **Elevation of an affected limb** is usually essential for successful therapy
- **I&D** recommended for abscesses (may not require ABX); **swab** purulent exudate

	Pediatric Dose	Adult Dose	Comments
EMPIRIC THERAPY FOR MSSA			
Cephalexin	50-100mg/kg/day PO ÷ QID	500mg PO QID	- **100%** of **MSSA** isolates in SHR [2015] & RQHR [2016] were sensitive to cephalexin & cloxacillin - consider cephalexin if type IV **penicillin allergy** e.g. rash
Cloxacillin	50mg/kg/day PO ÷ QID	500mg PO QID	
EMPIRIC THERAPY FOR MRSA, or MSSA with PENCILLIN ALLERGY (i.e. anaphylaxis)			
TMP/SMX	8-12mg/kg/day (TMP) PO ÷ BID if >1 month old	1-2 DS tab PO BID	- **94-100%** of **MRSA** isolates in SHR & RQHR are sensitive to TMP/SMX or doxycycline - **MSSA & PENICILLIN ALLERGY:** **92-100%** of **MSSA** isolates in SHR & RQHR are sensitive to TMP/SMX or doxycycline
Doxycycline	≥9 yr:4mg/kg/day PO ÷ BID	100mg PO BID	

TREATMENT EVIDENCE FOR BOTH NON-PURULENT & PURULENT CELLULITIS

Duration of therapy:

- For uncomplicated cellulitis (purulent & non-purulent), 5 days of therapy is as effective as 10 days providing clinical improvement by day 5. [IDSA 2014]
- Skin infections may worsen the first few days after I&D ± antibiotics are initiated. This worsening of the infection is part of the healing process & does not represent treatment failure. However, reassess management if systemic symptoms develop.
- Reassure the patient that full inflammation / symptom resolution (i.e. skin healing) may take 1 to 2 weeks after antibiotics are stopped.

Cephalexin ± TMP/SMX for Uncomplicated Cellulitis without an Abscess

- Adding TMP/SMX to cephalexin in outpatients with cellulitis without an abscess failed to provide additional benefit compared to cephalexin alone:
  - RCT with n=146 patients without diabetes, immunosuppression, peripheral vascular disease or hospitalizations
  - conducted in an area endemic for CA-MRSA; ~5% had nasal MRSA colonization
  - weight based dosing for both cephalexin (500-1000mg QID) & TMP/SMX (SS QID to DS QID) x 7-14 days, but mean doses & duration not reported
  - the difference in cure rate was not statistically significant [cephalexin alone 82% vs cephalexin + TMP/SMX 85%, risk difference 2.7% (95% CI -9.3% to 15%)]
  - progression to abscess & adverse events were also not statistically significant
- Empiric therapy with cephalexin monotherapy is reasonable.

Treatment Evidence for both Non-Purulent & Purulent Cellulitis continued

Clindamycin vs TMP/SMX for Uncomplicated Skin Infections

- Cure rates, tolerability & discontinuation rates were similar between clindamycin vs TMP/SMX in a small patient population:
  - RCT with n=524 outpatients with uncomplicated skin infections (~53% cellulitis, ~30% abscess & ~16% mixed)
  - swabs were obtained for suppurative lesions (57%): ~50% positive culture
    - ~41% *S. aureus* ~77% were MRSA, ~5% resistant to clindamycin
  - clindamycin 300mg TID vs TMP/SMX 2 DS tabs BID x 10 days
    - incision & drainage performed on all abscesses
  - the difference in cure rate was not statistically significant [clindamycin 89.5% vs TMP/SMX 88.2%, risk difference -1.2% (95% CI -7.6 to 5.1%)]
  - adverse events, including serious adverse events & discontinuation rates were similar between the groups
  - cure rates were similar when groups were stratified by cellulitis with or without an abscess
- In Saskatchewan, TMP/SMX or doxycycline are preferred over clindamycin due to resistance concerns & adverse events (clindamycin community-associated *C.diff* RR 3.92).

What dose of TMP/SMX should be used for *Staph aureus* skin infections?

- Recent evidence suggests that patients with an uncomplicated *S.aureus* skin infections & a BMI ≤40kg/m^2 can be successfully treated with a standard dose of TMP/SMX (1 DS tablet BID). Consider high-dose TMP/SMX (2 DS tablets BID) in individuals with a BMI>40kg/m^2. 1 double strength (DS) tablet = 160mg TMP / 800mg SMX
- References often recommend 1 to 2 DS tablets BID to QID, without guidance on selecting between the two doses. The most recent guidelines (2017 Sanford Guide) recommend 1 DS tablet BID with the caveat to use 2 DS tablets BID for patients with a BMI >40kg/m^2.
- Recent "larger" RCTs that compared TMP/SMX to *other* treatment modalities used high-dose (2 DS tabs BID). However, smaller observational studies that compared standard to high-dose TMP/SMX collectively suggest standard dose is appropriate for those with a BMI ≤40kg/m^2:
  - A 2011 prospective observational single center study concluded that high-dose TMP/SMX (2 DS tabs BID) failed to provide additional benefit in terms of clinical resolution compared to standard dose (1 DS tab BID) x 7-15 days in n=291 patients with MRSA skin infections (1 DS BID 75% vs 2 DS BID 73%, OR 0.96 [95% CI 0.76-1.2])
    - patients on high-dose TMP/SMX were more likely to have a trauma, & receive incision & drainage (the % of patients with an abscess was NS between the two groups)
    - results were similar for those who underwent I&D
    - both treatment groups had a similar BMI (30 vs 28kg/m^2, p=NS)
  - A small 2012 retrospective observational single center study (n=102) identified that morbidly obese patients (BMI>40kg/m^2) were at greater risk of clinical failure when prescribed the standard dose of TMP/SMX (1 DS tab BID):
    - hospitalized for cellulitis with or without abscess
    - 94.8% received empiric IV antibiotics prior to stepping down to oral agents
- **Safety:** hyperkalemia & nausea are dose-dependent, but the risk of SJS is not

Clinical Q&A

When should I consider MRSA decolonization?

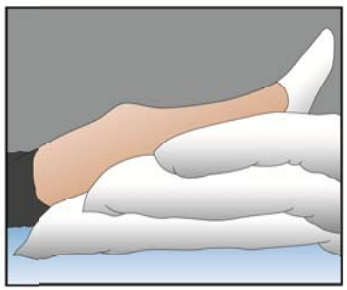
- Routine decolonization is **not** recommended in the community due to a lack of short & long-term efficacy, and concerns regarding antibiotic resistance.
- Decolonization is of limited benefit as the relapse rate is very high (up to 75% at one year post decolonization), & even higher if the risk factors are not addressed at the same time of decolonization (e.g. poor hygiene, overcrowding).
- Consider patient referral to Infection Control &/or an Infectious Disease Specialist for decolonization.
- There may be some utility in patients who have recurrent infections (≥3 per 6 months) despite optimal wound care & proper hygiene, ongoing transmission among household contacts & other close contacts, or in those who are frequently hospitalized and have a high risk of complications if infection occurs.
  - Note, theoretically, decolonization may result in replacement of host MRSA strain with a more virulent subtype

How to obtain a specimen for culture & sensitivity

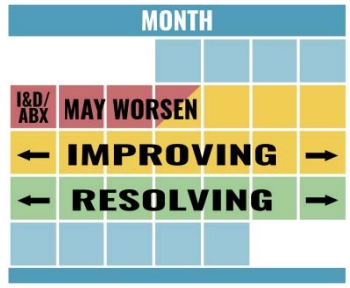
- consider swabbing moderate to severe **purulent** skin infections on the initial visit
  - routine swabbing of **non-purulent** skin infections is **not** recommended as cultures will grow normal skin flora
- ensure to swab the inside of the abscess cavity &/or purulent drainage / exudate, and not the superficial skin over the abscess
- label with specimen with the location & type of wound (e.g. "abscess, lower left shin")
- if the culture & sensitivity indicates a bacterial infection, avoid initiating antibiotics if the infection is improving (i.e. incision & drainage alone results in clinical cure in ~80% of cases)
- see RxFiles Online Extras for additional information on the incision & draining procedure and culturing skin infections

3 NON-DRUG MEASURES FOR SUCCESSFUL TREATMENT OF SKIN INFECTIONS

incision & drainage



elevate affected limb



allow 2 to 3 weeks for inflammation to resolve

Skin & Soft Tissue Infections Abbreviations

BMI=body mass index **C&S**=culture & sensitivity **CA-MRSA**=community associated MRSA **CDC**=Center for Disease Control **CI**=confidence interval **DS**=double strength **g**=generic **GAS**=Group A Streptococcus **HCA-MRSA**=health care associated MRSA **I&D**=incision & drainage **IDSA**=Infectious Diseases Society of America **MRSA**=methicillin-resistance *Staphylococcus aureus* **MSSA**=methicillin-sensitive *Staphylococcus aureus* **N** or **n**=number **NS**=non-statistically significant **OR**=odds ratio **OTC**=over-the-counter **RCT**=randomized controlled trial **RQHR**=Regina Qu'Appelle Health Region **RR**=relative risk **rxn**=reaction ***S.aureus***=*Staphylococcus aureus* **SHR**=Saskatoon Health Region **SJS**=Stevens Johnson Syndrome ***Staph***=*Staphylococcus* ***Strep***=*Streptococcus* **SSTI**=skin & soft tissue infection **TMP/SMX**=trimethoprim-sulfamethoxazole **WBC**=white blood count

APPENDIX C

A. INCISION AND DRAINAGE (I&D) PROCEDURE

Adapted from US Federal Bureau of Prisons MRSA CFG April 2011

Abscesses are localized infections of tissue marked by a collection of pus surrounded by inflamed tissue. Abscesses may be found in any area of the body; those requiring more urgent attention are found on the extremities, face, buttocks, breast, perianal area, axilla, groin. Abscesses begin when the normal skin barrier is breached, and microorganisms colonize the underlying tissues. Causative organisms commonly include *Streptococcus sp.*, *Staphylococcus sp.*, enteric bacteria (perianal abscesses), or a combination of anaerobic and gram-negative organisms.
Abscesses resolve by drainage. Smaller abscesses may resolve with conservative measures (warm soaks) to promote spontaneous drainage. Larger abscesses will require incision to drain them (I & D) as the increased inflammation, pus collection, and walling-off of the abscess cavity diminish the effectiveness of antibiotic treatment. Healing following I & D should progress from the inside of the abscess outward to the incision site. For larger abscesses this may require a gauze packing to promote healing from the inside outward (See Part B below: Role of Packing for an Abscess)

NOTE:

- Extremely large abscesses that require extensive incision, debridement, or irrigation are best done in operating room.
- Deep abscesses in very sensitive areas (labial, supralevator, ischiorectal, perirectal) often require a general anesthetic to obtain proper exposure.
- Abscess in the hands or feet are best drained by a surgeon. Deep palmar abscesses are a surgical emergency.
- Abscesses in the triangle formed by the bridge of the nose and the corners of the mouth should generally be treated with warm compresses and aggressive antibiotic therapy.
- Abscesses located near major vessels must be differentiated from aneurysms before I & D is performed to avoid fatal hemorrhage. The distinction is made through aspiration with a large bore needle, or with ultrasound guidance.

PROCEDURE

- **The information below applies to an abscess within the skin and subcutaneous tissue that is palpable.**
- **Obtain informed consent.**
- **Use Routine/Standard Infection Control Precautions, and sterile technique.**

1. Infiltrate local anesthetic, allowing 2–3 minutes for anesthetic to take effect. Remember that tissue around an abscess is acidotic and local anesthetic is less effective. Consider doing a field block.
2. Incise over abscess with the scalpel blade, cutting through the skin into the abscess cavity. Follow skin fold lines whenever possible while making the incision. The incision should be sufficiently wide to allow the abscess to drain and to prevent premature closure of the incision.
   For smaller abscesses requiring incisions, a stab or cruciate incision should be adequate. Some refer to this as a puncture or stab technique since the operator inserts the tip of the scalpel directly into the center of the abscessed tissue without making a linear incision. If a culture is being obtained, use the culture swab to take culture of abscess contents, swabbing inside the abscess cavity—not from the superficial skin over the abscess.
3. Use a hemostat or sterile cotton-tipped applicator to gently explore the abscess cavity to break up any loculations within the abscess.
4. Loosely pack the abscess cavity with the packing (if indicated).
5. Place gauze dressing over the wound, and tape in place. Topical antibiotic is not required.
6. Schedule patient to return for review within 24–48 hours post-procedure. Depending upon the location and size of the abscess, arrange for the packing material to be changed daily.
7. Pain from the site may require acetaminophen or nonsteroidal anti-inflammatory drugs; narcotics are rarely needed.

Following I & D of any abscess:

- Routine use of oral antibiotics after uncomplicated I & D is NOT recommended. Antibiotics have a role for patients with complicated abscesses (such as those with systemic symptoms), immunocompromised patients, and for abscesses with significant surrounding cellulitis or in areas difficult to drain, such as the hand.
- The site should be observed for signs of recollection of pus or cellulitis.
- Complications of an inadequately treated abscess include bacteremia and septicemia.
- In persons who are immunocompromised, particularly people with diabetes or peripheral arterial disease, an abscess on an extremity can be complicated by severe cellulitis or gangrene, with potential loss of the affected extremity.

Post-Procedure Patient Education.

- Patients should be instructed to watch for the following symptoms:
  - Recollection of pus in the abscess
  - Fever and chills
  - Increased pain and redness
  - Red steaks near the abscess
  - Increased swelling

References:
Dirksen DJ. Incision and drainage of an abscess. In: Pfenninger JL, Fowler GC, eds. *Procedures for primary care physicians*. St. Louis: Mosby; 2003:50–53.
Kronful R. Technique of incision and drainage for skin abscess. *UpToDate*. May 13, 2009;17.2
Singer AJ, Thode HC Jr. Systemic antibiotics after incision and drainage of simple abscesses: a meta-analysis. Emerg Med J. 2013 May 18.

B. ROLE OF PACKING FOR AN ABSCESS

Packing of wounds – there is no scientific evidence to support packing of wounds after I&D of a simple cutaneous abscess.
Studies (RCT) looking at outcomes from packing of simple abscesses are limited in number and of small size. O'Malley *et al* demonstrated no difference in outcomes in patients who had I&D, standard wound irrigation and packing or no packing, however the packing group reported more pain and use of analgesics. There were no significant differences between groups in need for second intervention at 48 hours.
Packing of cutaneous abscesses is not usually done in developing countries with no significant problems. Clinical follow-up at 48 hours after I & D of simple cutaneous abscess is important whether wound is packed or not.

Reference:
O'Malley GF etal. Routine Packing of Simple Cutaneous Abscesses Is Painful and Probably Unnecessary Academic Emergency Medicine 2009; 16:470–473

C. CULTURING CELLULITIS

The diagnosis of cellulitis is based on the clinical features. Cellulitis associated with furuncles, carbuncles, or abscesses is usually caused by *S.aureus*. In contrast, cellulitis that is diffuse or unassociated with a defined portal is most commonly caused by streptococcal species.

- For outpatients with **non-purulent cellulitis**, **cultures** will usually grow normal skin flora and are therefore **not routinely recommended**.
  - Empirical therapy for infection due to beta-hemolytic streptococci is recommended.
  - Empirical coverage for MRSA may be considered in those with systemic signs and symptoms and is recommended in patients who do not respond to initial therapy.

- For outpatients with **purulent cellulitis** in the absence of a drainable abscess, **swab purulent drainage or exudate and send for culture.**
  - Empirical therapy for infection due to beta-hemolytic streptococci is not likely necessary.
  - Empirical therapy for MRSA may be considered pending culture results.

Other microbiological investigations including aspiration and punch biopsies are not routinely recommended because results are rarely positive. Blood cultures are recommended when there are signs and symptoms of systemic illness.

Reference:
Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant Staphylococcus aureus Infections in Adults and Children. Clinical Infectious Diseases 2011; 52:1-38

BETA-LACTAM ALLERGIES [1-3]

Of all the drugs on the market, beta-lactams (and penicillin in particular) seem to be most implicated in allergic reactions. However, such allergy is over-reported.

Clinical Pearls

1. Delayed rashes caused by penicillin, **if after first few doses/days & no itchiness/hives**, are not typically indicative of a true IgE-mediated allergy. A beta-lactam, such as a cephalosporin, can usually be given.
2. When possible, refer patients with uncertain penicillin allergy for **skin testing**. Skin testing is especially helpful when the allergy history is unclear, when the reaction took place >10 years ago, or when the reaction occurred days rather than hours after taking the antibiotic.
3. When the risk of true penicillin allergy is low, **a graded challenge** using a cephalosporin with a dissimilar side-chain is appropriate.

Definitions

- **Beta-lactams**: group of antibiotics with a distinctive beta-lactam ring; includes penicillins, cephalosporins, and carbapenems. Allergy may occur to either the beta-lactam ring (in which case a patient is allergic to all beta-lactams) or to the unique side chain (in which case the allergy is only to specific agents).
- **IgE**: immunoglobulin type E antibody. After encountering a specific antigen, IgE antibodies can trigger an immune response.[10]
- **"True" IgE-mediated allergy:** potentially life-threatening reaction; also known as a type-1 immediate hypersensitivity reaction. Symptoms are described below in "Management of Penicillin Allergy". Anaphylaxis describes the most severe form of reaction.[11]
- **Graded challenge**: some variation in approaches, but often a small dose of a potential allergen (e.g. 10% of the full dose) is given, followed by the full dose 1 hour later.[7] {NOTE: **in the in-patient setting**, inappropriate consideration of penicillin allergy resulting in use of vancomycin or clindamycin may create suboptimal outcomes. Often a beta-lactam can be used. Take advantage of the inpatient status to confirm/monitor as necessary.}
- **Desensitization**: similar to the graded challenge, but at a slower pace (e.g. starting at 1/10,000th of the full dose). A sample protocol for an oral desensitization is here: www.cdc.gov/std/tg2015/pen-allergy.htm and an intravenous approach may be found in the **Online Extras** 💻.
- **Penicillin skin-testing**: pricking the skin with a minute quantity of penicillin; if a localized reaction not observed, an IgE-mediated allergy is unlikely.[5]

How likely is a beta-lactam allergy?

10,000	**In a given group of 10,000 patients:**
1,000	⇨ will **report** they have a penicillin allergy,[1]
<100	⇨ will **have** a true IgE-mediated penicillin allergy,[2]
1 to 3	⇨ will have cephalosporin cross-reactivity,[3]
1	⇨ will have anaphylaxis when given penicillin.[4]

Table 1: Factors that decrease the likelihood of a true allergy

Skin test is negative: this provides a 97-99% certainty that the patient is not allergic.[5]
Age: 80% of patients with a reaction that occurred >10 years ago will no longer be allergic to penicillin.[1]
Administration: reactions reported from oral administration are less likely to be true allergies.
Symptoms: see below for how IgE-mediated symptoms differ from other beta-lactam reactions.
Timing: if reaction occurred after days to weeks of taking antibiotic, it is unlikely to be IgE-mediated.[11]

Management of Penicillin Allergy

After a reaction to penicillin, can a beta-lactam be prescribed in the future? The answer requires accurate differentiation between three types of beta-lactam adverse reactions.

Penicillin Adverse Event	Serious Penicillin Adverse Event	True IgE-Mediated Penicillin Allergy
e.g. rash, GI upset, headache. A diffuse rash, which is not itchy, occurs in ≤10% of patients taking penicillin, usually after 2-5 days of therapy, and may last several weeks.[12] These reactions are not IgE-mediated.	e.g. Stevens-Johnson syndrome, interstitial nephritis, hemolytic anemia, serum sickness*. These reactions usually occur >72hrs after beta-lactam dose.[11] They are not IgE-mediated.	At minimum, presents as an itchy rash or hives. More severe symptoms include angioedema, hypotension, or bronchospasm. These reactions can be life-threatening and usually occur <1hr after taking a beta-lactam dose.[9-11] Anaphylaxis describes the most severe form of reaction.
• An uncomplicated rash, a headache, or GI upset is not IgE-mediated, and so a cephalosporin or different penicillin may be prescribed. • **Amoxicillin** has a high risk of rash when given during some viral infections, such as infectious mononucleosis (e.g. Epstein-Barr virus, cytomegalovirus); however this is not an allergy.[8]	• All beta-lactams are contraindicated. Prescribe an alternative agent. • Skin testing, desensitization, and graded challenges are all **potentially harmful and not recommended**.[8]	1. **Skin test if possible**, especially if reaction was many years ago. **If the skin test result is negative**, cephalosporins may be given safely & pencillins may be given with minimal risk.[AAAAI/ACAAI (D)] Consider administering the first dose via graded challenge if previous severe reaction. **If the skin test result is positive, OR skin testing is unavailable**, a cephalosporin graded challenge may be appropriate if patient factors described in Table 1 point away from IgE-mediated. A cephalosporin with a dissimilar side chain is preferred (see below).[12-15] 2. Otherwise, prescribe an alternative agent. 3. If no good alternative agents, initiate a cephalosporin desensitization procedure.
	Similar side chains (Canada):	penicillin VK and cefoxitin; amoxicillin, ampicillin, cefadroxil, cephalexin, cefaclor, and cefprozil; cefepime, ceftriaxone, and cefotaxime; cefuroxime and cefoxitin; ceftazidime and aztreonam Of note: **cefazolin** has a unique side chain dissimilar to all other beta-lactams

Additional Information:

- **Cephalosporin allergy management**: similar to penicillins, but less studied.
  - ❶ GI upset, headache, or rash (without hives/itch) are not signs of true allergy and a beta-lactam may be prescribed;
  - ❷ Serious adverse events (e.g. Stevens-Johnson syndrome, interstitial nephritis, hemolytic anemia, serum sickness) are contraindications to any beta-lactam;
  - ❸ If allergy is likely IgE-mediated, skin test (if possible) using a cephalosporin with a different side chain than the cephalosporin that previously reacted. **If no reaction**, give a graded challenge; **if reaction, or if skin testing not available**, use an alternative agent (or desensitization).[12-15]
- **Skin tests in Saskatchewan are available via referral** (currently <6 month waiting list [2017]). Encouraged for all with questionable allergies. Cost to patient: ~$20.
- **Cross-sensitivity data**: Cephalosporin and penicillin cross-sensitivity rate was at first thought to be up to 10%; however this was due to penicillin contamination in cephalosporin products and the true rate is likely 1-3%.[3,7] Evidence suggests that carbapenems have a ~1% cross-reactivity with penicillins, and are appropriate in penicillin allergies any time a cephalosporin could be prescribed.[16] Aztreonam does not typically have cross-reactivity with penicillins, and so can be prescribed

***Serum sickness reactions:** These are more common than the other serious reactions listed. Generally, these occur after 7-10 days of therapy and relate to immune complexes of IgG. Symptoms include urticarial vasculitis, renal dysfunction and joint pain. Skin testing is not helpful. Challenges and desensitization are contraindicated.

Antibiotics: Potential Harms

Antibiotics are a valuable resource and judicious use is very important. For many serious infections (e.g. pneumonia, bacterial meningitis, sexually transmitted infections) the benefits of antibiotics clearly outweigh potential harms. However, for conditions that are primarily viral (e.g. pharyngitis, acute sinusitis, acute bronchitis), the benefits are minimal and likely outweighed by harms. Of note: antibiotic-related adverse drug events account for 1 out of every 5 visits to the Emergency Department.[1]

Common Adverse Events

Overall NNH = 8-12 **Yeast infection NNH = 23**

- In a meta-analysis (10 trials, 2450 patients) comparing antibiotics to placebo for acute rhinosinusitis, common adverse events (such as **nausea**, **vomiting**, **diarrhea**, or **abdominal pain**) occurred in 27% of patients on antibiotics versus 15% on placebo (NNH = 8-12).[2,5] The antibiotics used in this meta-analysis included **penicillins**, **macrolides**, and **tetracyclines**. Trials examining other populations have found similar numbers of adverse events.[3,4,5]
- A recent meta-analysis comparing amoxicillin or amox/clav to placebo found risk of **yeast infection** (candidiasis) ~ 8x higher in those on antibiotics (NNH = 23).[6]

Allergic Reactions

NNH from 20 (rash, hives) to 10,000 (anaphylaxis)

Allergic reactions can occur with any antibiotic; **penicillin** in particular is well studied. About 5-10% of patients will self-report a penicillin allergy;[7,8] however the vast majority of these reactions are delayed reactions, occurring days to weeks after initiating therapy, and do not typically indicate a true allergy.[9] Anaphylaxis occurs in about 0.01% of patients taking penicillin; about 10% of these reactions are fatal (i.e. 0.001% of all patients prescribed penicillin).[10,11,12]

Serious Adverse Events

NNH from 300 to 30,000

Rare but serious adverse events are associated with all antibiotics. Large, long-term randomized controlled trials are uncommon, and so it is difficult to put a precise estimate on how prevalent these events are. However, some adverse events include:

- ***Clostridium difficile* infection**: associated most often with **clindamycin** (RR≈4), cephalosporins, and fluoroquinolones; risk varies depending on patient factors.[13,14,15]
- **Stevens Johnson Syndrome, Toxic Epidermal Necrolysis, & other severe skin reactions**: these events occur a few times per 100,000 antibiotic prescriptions.[16] Cotrimoxazole in particular has a higher association than most other antibiotics.[17]
- **QT prolongation**: associated most often with macrolides (esp. **clarithromycin** and **erythromycin**) and fluoroquinolones (esp. **levofloxacin** and **moxifloxacin**). Risk of QT prolongation is also dependent on other factors (e.g. cardiac, metabolic, other drugs, etc.). See RxFiles QT Prolongation page 32 (11th Ed).
- **Tendon rupture with fluoroquinolones**: one large cohort study found a risk of 3.5% for tendon rupture in adults over the age of 65.[18]
- **Hyperkalemia with cotrimoxazole**: in older adults taking medications which can raise potassium (such as **ACEIs**, **ARBs**, **spironolactone**, or **NSAIDs**), **cotrimoxazole** was associated with sudden death (NNH ≈ 300).[19,20]
- **Contraceptive failure/drug interaction?** Although this is thought to be unlikely, there is a small but real risk & a backup birth control method is always recommended.

Other

There are many other less common harms than can be covered here! e.g. serum sickness like reactions, pulmonary fibrosis with nitrofurantoin, tooth discoloration with tetracyclines

Antibiotic Resistance

NNH as low as 1??? Every course of antibiotic is likely to result in some emerging resistance which could affect the next choice of antibiotic regimen for that individual, especially if within 3 months of the previous antibiotic. Of course the NNH for catastrophic resistance would be much higher.

Resistance to an antibacterial can develop quickly. For example, strains of *Streptococcus pneumoniae* resistant to **levofloxacin** were documented in the same year levofloxacin was introduced to the market.[21] Rare, but worrisome, reports of bacteria resistant to every available antimicrobial can be found in the literature.[22] The good news is that when prescribing patterns change, resistance rates decline.[23,24]

Quotes from the team ☺: *Harms speak louder when there is little or no benefit to offset them!*

www.RxFiles.ca/ABX

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 DURICEF, g 500mg cap ✗▼ P L		**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 $P_1P_{2,3}$ L	• **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 $P_1P_{2,3}$ L	• **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 $P_1P_{2,3}$ L	• **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 ☎ ▼ $P_1P_{2,3}$ L	• **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 $P_{1,3}$ L	• **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 $P_1P_{2,3}$ L	• **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.rghealth.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]

CASE DISCUSSIONS

ACUTE UNCOMPLICATED CYSTITIS

A 25 year old female presents with a 36-hour history of dysuria, frequency and urgency. She does not have any fever or other generalized symptoms.

➼ **Med Hx**

- medical history unremarkable
- sexually active with 1 partner
- medications: an oral contraceptive
- no hx of antibiotics in last 5 years
- no allergies

➼ **Physical Examination**

- suprapubic discomfort
- no costovertebral angle tenderness
- no fever or chills

➼ **Treatment Options** (alphabetical)

☐ Amoxicillin	x _____ days
☐ Amox/Clavulinic	x _____ days
☐ Cephalexin	x _____ days
☐ Ciprofloxacin	x _____ days
☐ Fosfomycin	x _____ days
☐ Nitrofurantoin	x _____ days
☐ Norfloxacin	x _____ days
☐ TMP/SMX	x _____ days
☐ Trimethoprim	x _____ days

➼ **What if...**

- she had one previous similar episode 6 weeks earlier?
- she has a previous hx of 5 such infections in the past year?
- she returns in 5 days with new & worsening symptoms?

SKIN & SOFT TISSUE INFECTION

A 25 year old male presents with pain and inflammation to his lower leg. This has evolved over a few days following a scrape while doing yard work. He has been active at work and in sports since the accident, but his leg is more painful today.

➼ **Med Hx**

- generally healthy, a non-smoker
- "allergy to penicillin" (he had a rash while on amoxicillin as a child)
- not taking any medication

➼ **Physical Examination**

- distal 1/3 leg: warm, red, swollen 8 cm area of skin surrounding a small dry abrasion above medial malleolus; no fluctuation; no lymphangitis
- afebrile
- appearance consistent with cellulitis

➼ **Treatment Options** (alphabetical)

☐ Cephalexin	x _____ days
☐ Clarithromycin	x _____ days
☐ Cloxacillin	x _____ days
☐ Doxycycline	x _____ days
☐ Other	x _____ days
☐ Polysporin topical	x _____ days
☐ TMP/SMX	x _____ days
☐ Rest, elevate leg	☐ Medical certificate for work

➼ **What if...**

- he has signs of an abscess?
- he is on the wrestling team?
- he is febrile?

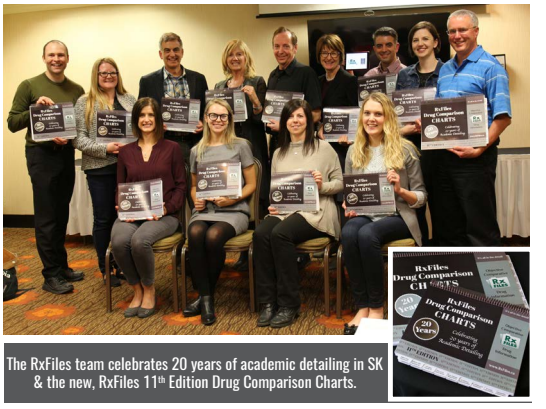
Coming up Fall 2017: OPIOIDS

RxFiles: Celebrating 20 Years

As of April 2017, we are celebrating 20 years of academic detailing in Saskatchewan. A lot has changed over two decades, and we have grown with the changes. One thing that remains the same is our commitment to bring evidence to practice through friendly, informative face to face discussions. What you see in print is just a tool to support these discussions and help them to inform practice long after they are done. Thank you to everyone in Saskatchewan who has supported us.

Your input and participation is at the heart of RxFiles!!!

We value: quality evidence, clinical experience, cost effectiveness, practical considerations including patient & societal values. It's all in the detail!



The RxFiles team celebrates 20 years of academic detailing in SK & the new, RxFiles 11th Edition Drug Comparison Charts.

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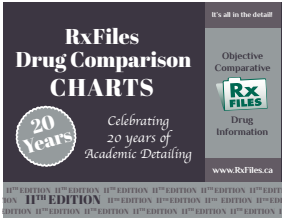

Drug Comparison Charts
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Objective & Evidence-based Drug Information

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