



Tips on Avoiding the Most Common Scenarios for Antibiotic Misuse

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Disclosures

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Session Objectives

- Describe antibiotic stewardship: what it is and why it's important
- Recognize application of stewardship principles to antibiotic prescribing best practices (right drug, right route/dose, right duration)
- Demonstrate practical applications of antibiotic stewardship to the top clinical scenarios where antibiotics can be misused including pneumonia, urinary tract infections and skin/soft tissue infections
- Identify the utility and use of novel antibiotics that target skin and soft tissue infections, including Dalbavancin and Oritavancin

Antibiotic Stewardship



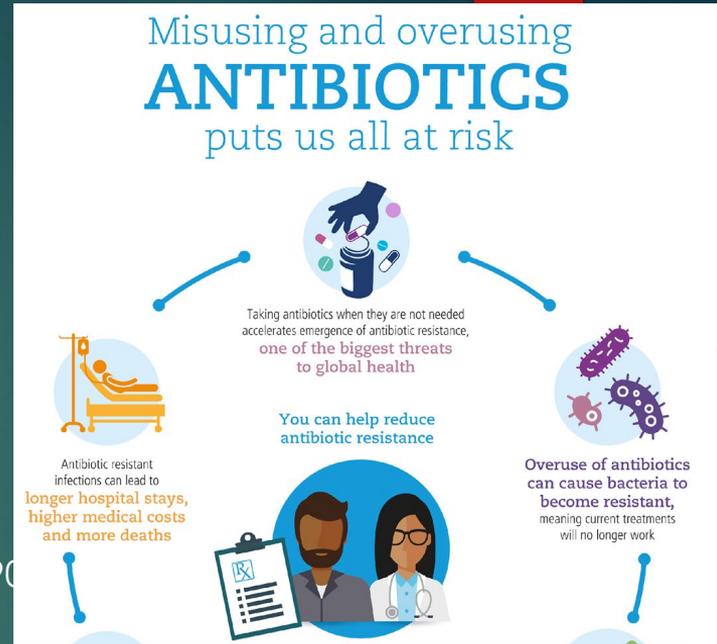
What is stewardship?

“Antimicrobial stewardship refers to coordinated efforts of an **interdisciplinary team** of individuals improving and measuring the **appropriate use of antimicrobials** through promoting **optimized drug selection, dose selection, duration, and route of administration.**”

-University of Colorado Hospital Antibiotic Stewardship Mission Statement

Why Should We Care?

- **Increased Cost**
- **Adverse Effects** - Reactions from antibiotics cause 1 to the Emergency Department
 - *C. difficile* infections (CDI) - In 2017 there were 223,900 the U.S. and at least 12,800 deaths



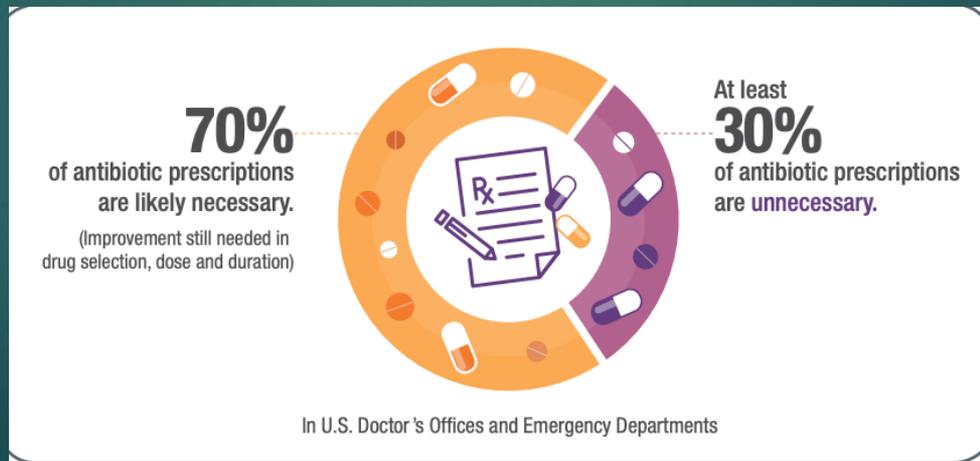
	% increased relative risk of developing resistance		
	Cefepime	Meropenem	Piperacillin-Tazobactam (Zosyn)
Each additional day of exposure	8%	2%	8%

Outpatient Antibiotic Prescribing Data

~47 million antibiotic courses each year are prescribed for infections that **don't require antibiotics**

In 2016, 270.2 million antibiotic prescriptions were written in the United States =

Enough antibiotic courses for five out of every six Americans (on average) to receive an antibiotic prescription!



Inpatient Antibiotic Use

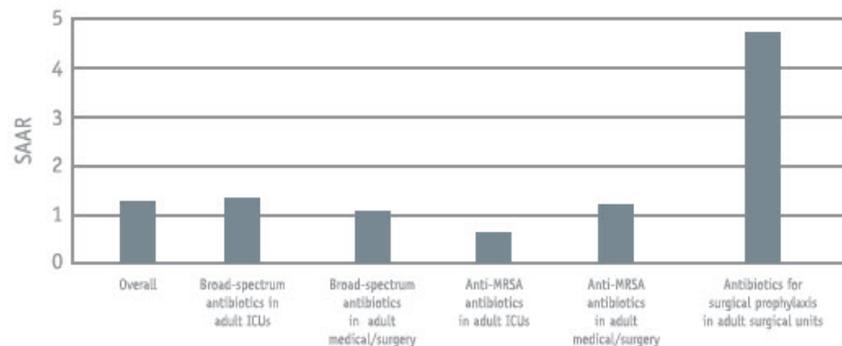
1/3 of hospital antibiotic prescriptions involve potential prescribing problems:

- Lack of proper testing/evaluation for infection
- Prescribing an antibiotic when it is **not** needed*
- Providing an antibiotic for **too long**

*>50% of hospital antibiotics are prescribed for **three** infections:

- Lower respiratory tract infections
- Urinary tract infections
- Skin and soft tissue infections

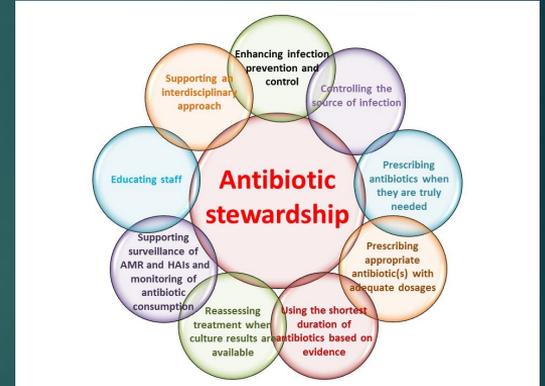
Ratio of observed to expected antibiotic use (SAAR*) by category and unit type in one Intermountain Healthcare facility, Quarter 1, 2016.



*Standardized Antimicrobial Administration Ratio. A SAAR value of less than 1 indicates less than expected antibiotic use, and a value greater than 1 indicates higher than expected antibiotic use.

Best Practices for Antibiotic Use

- **Right drug**
 - Empiric vs Definitive/Directed vs Prophylactic therapy
 - Do not prescribe an antibiotic for a viral infection or colonization!
 - Goal is to use the **narrowest** effective agent
- **Right route and dose**
 - Switch from IV to oral routes when appropriate
- **Right duration**
 - Use the shortest, effective duration



Understand the pharmacokinetics and pharmacodynamics of the antibiotics being prescribed

Best Practices = Use of Resources

Antibacterials	SANFORD GUIDE												
	Penicillin G	Penicillin VK	Nafcillin	Oxacillin	Clasoxillin	Fludoxacillin	Dicloxacillin	Ampicillin	Amoxicillin	Amox-Clav	Amp-Sulb	Pip-Tazo	Carbapenems
Aerobic gram-pos cocci													
<i>E. faecalis</i> (S)	++	0	0	0	0	0	0	++	+	+	+	+/-	+/-
<i>E. faecium</i> (S)	+/-	0	0	0	0	0	0	+/-	+/-	+/-	+/-	0	0
<i>E. faecalis</i> (VRE)	+/-	0	0	0	0	0	0	+/-	+/-	+/-	+/-	0	0
<i>E. faecium</i> (VRE)	+/-	0	0	0	0	0	0	+/-	+/-	+/-	+/-	0	0
<i>S. aureus</i> MSSA	+/-	++	++	++	++	++	++	+/-	+/-	+	+	+	+
<i>S. aureus</i> HA-MRSA	0	0	0	0	0	0	0	0	0	0	0	0	0
<i>S. aureus</i> CA-MRSA	0	0	0	0	0	0	0	0	0	0	0	0	0
Staph coag-neg (S)	+/-	+/-	++	++	++	++	++	+/-	+/-	+	+	+	+
Staph coag-neg (R)	0	0	0	0	0	0	0	0	0	0	0	0	0
<i>S. epidermidis</i> (R)	0	0	0	0	0	0	0	0	0	0	0	0	0
<i>S. epidermidis</i> (S)	+/-	+/-	++	++	++	++	++	+/-	+/-	+	+	+	+
<i>S. lugdunensis</i>	+/-	+/-	++	++	++	++	++	+/-	+/-	+	+	+	+
<i>S. saprophyticus</i>	+/-	+/-	+	+	+	+	+	+/-	+/-	++	+	+	+
Strep. anginosus gp	++	++	+	+	+	+	+	+	+	+	+	+	+
Strep. pyogenes (A)	++	++	+	+	+	+	+	+	+	+	+	+	+
Strep. agalactiae (B)	++	++	+	+	+	+	+	+	+	+	+	+	+
Strep. gp C,F,G	++	++	+	+	+	+	+	+	+	+	+	+	+
Strep. pneumoniae	++	++	+	+	+	+	+	+	+	+	+	+	+
Viridans Strep.	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-
Aerobic gram-pos bacilli													
<i>Arcanobacter</i> sp	+	+	?	?	?	?	?	+	+	+	+	+	+
<i>C. diphtheriae</i>	++	++	0	0	0	0	0	+	+	+	+	?	?
<i>C. jejekulum</i>	0	0	0	0	0	0	0	0	0	0	0	0	0
<i>L. monocytogenes</i>	+	0	0	0	0	0	0	++	+	+	+	?	?
<i>Nocardia</i> sp.	0	0	0	0	0	0	0	0	0	+/-	?	?	?
Aerobic GNB - Enteric													
<i>Aeromonas</i> sp.	0	0	0	0	0	0	0	0	0	0	+/-	+/-	+

	% Susceptible																		
	Isolates (n)	AMIKACIN	TORBRAMYCIN	GENTAMICIN	AMPICILLIN	AMOX-CLAV	AMP-SULB	CEFAZOLIN (Non-Urine Breakpoint)	CEFURONIME	CEFTRIAXONE	CEFTAZIDIME	CEFEPIME	PIPERACILLIN-TAZOBACTAM	AZTREONAM	MEROPENEM	ERTAPENEM	CIPROFLOXACIN	TETRACYCLINE	BACTRIM
Inpatient Gram Negative (UCHealth Metro - all sources and locations, July 2017 - July 2018)																			
<i>E. coli</i>	1848	99	89	90	50	83	55	71	87	91	93	93	96	92	99	99	77	73	73
<i>Klebsiella</i> spp.	576	100	95	96		90	72	70	86	92	94	95	91	93	98	98	92	87	89
<i>K. pneumoniae</i>	429	100	94	96		92	80	83	87	94	94	95	95	95	99	99	91	84	88
<i>K. oxytoca</i>	127	100	97	97		80	40	20	78	85	94	94	81	85	98	98	94	93	93
<i>Proteus</i> spp.	144	100	89	91	73	94	87	1	89	94	98	96	99	97	100	100	77		81
<i>P. mirabilis</i>	133	100	89	91	78	95	87	2	95	95	98	96	98	98	-	100	76		81
<i>Enterobacter</i> spp. ¹	299	99	98	99						68	71	85	72	72	99	89	98	90	94
<i>Citrobacter</i> spp. ¹	93	100	95	96		31	30	23	30	73	77	94	84	77	99	97	95	88	92
<i>C. freundii</i> ¹	60	100	93	93						63	67	90	77	70	98	95	92	83	93
<i>C. koseri</i>	26	100	100	100		88	84	81	84	84	96	100	96	96	100	100	100	96	100
<i>Serratia</i> spp. ¹	60	98	71	97						90	93	93	96	96	96	96	97	0	-
<i>Pseudomonas aeruginosa</i>	334	97	97	-						93	89	89	76	88			81		
<i>Acinetobacter</i> spp.	30	97	93	97		100 ²				87	93	90	-	97			96	0	90
<i>Stenotrophomonas maltophilia</i>	53										-	-					87	²	96

Grey boxes indicate organism has intrinsic resistance to the corresponding antimicrobial; boxes w/ hashes indicate organism may be susceptible, but insufficient data/numbers to report

¹*Citrobacter freundii* (not *hoseri*), *Enterobacter*, and *Serratia* have the potential to inducibly produce AmpC beta-lactamase and become resistant to 3rd generation cephalosporins, aztreonam, and piperacillin-tazobactam on therapy. Use these agents with caution. Failure rates appear highest with *Enterobacter* >> *Citrobacter* >> *Serratia*. Cefepime and carbapenems appear to be stable in the presence of high-level AmpC production.

²Minocycline has good activity against most *Stenotrophomonas* isolates

³Sulbactam is the active component against *Acinetobacter* spp. Use of higher doses 18-27g/day total (3g q3-4h or 9g q8h) necessary depending on infection source/severity, and combination usually needed for

Knowledge Test #1

A 52-year-old-female was admitted 2 days ago with fever and a productive cough. Imaging and labs confirmed a diagnosis of *Streptococcus pneumoniae* pneumonia and the patient was initiated on IV Ceftriaxone 2G daily. The patient is clinically improving, has been afebrile for 48 hours and is ready for discharge.

Which duration of therapy would be the most appropriate given prior treatments and current clinical status?

- A. 3 days
- B. 10 days
- C. 5 days
- D. 7 days

Community Acquired Pneumonia

2007 IDSA/ATS suggested minimum **5 days** of treatment, in clinically-stable patients who have been afebrile for 48-72 hours

Non-inferiority RCT comparing 5 days vs physician choice in hospitalized adult patients with CAP

Outcome	Control Group	Intervention Group	P Value
Intent-to-Treat Analysis			
Total No. of participants	150	162	
Clinical success, No. (%)^a			
At day 10	71 (48.6)	90 (56.3)	.18
At day 30	132 (88.6)	147 (91.9)	.33
CAP symptom questionnaire score, mean (SD)^b			
At day 5	24.7 (11.4)	27.2 (12.5)	.10
At day 10	18.6 (9.0)	17.9 (7.6)	.69

Knowledge Test #2

A 70 yo female with PMH of HTN and OA is admitted to the hospital for hip arthroplasty. On POD #3 she develops vomiting, constipation, and headache without complaints of dysuria, incontinence, urgency, frequency, or flank pain.

VS: HR: 76, BP 146/82, Temp 36C, O2 sat 97%

Exam: - CVA tenderness, - suprapubic tenderness, + absence of bowel sounds

UA pertinent for:

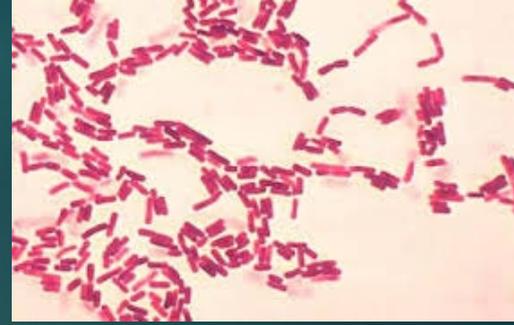
+Nitrites, 6-10 wbc/HPF, + Leukocyte esterase, Frequent Squamous Cells

Urine cx: >100,000 CFU/ml of Escherichia coli (S-SMX/TMP, S- Carbapenems, R - Nitrofurantoin)

Based on this presentation, would you:

- Treat with 5 days of SMX/TMP 1DS PO BID
- Treat with 3 days of SMX/TMP 1DS PO BID
- Treat with 3 days of Ertapenem 1G IV daily
- No treatment → pursue further workup for other causes

Asymptomatic Bacteriuria (ASB)



“Antimicrobial treatment of ASB has been recognized as an important contributor to inappropriate antimicrobial use, which promotes emergence of antimicrobial resistance.”

Infectious Disease Society of America (IDSA) updated guidelines on asymptomatic bacteriuria in 2019

- **Definition:** ASB is the presence of $>100,000$ colony-forming units (CFU)/mL of bacteria in properly collected urine in a patient who has no localizing urinary symptoms eg, dysuria, urinary frequency or urgency, or suprapubic pain

When to Test and Treat



Healthy **non pregnant** women:

- Prevalence of ASB in healthy, premenopausal women: 1% to 5%
- Women with ASB may be at increased risk of symptomatic UTI BUT ..
 - No evidence to suggest that episodes of symptomatic UTI are attributable to the ASB
 - ASB, even when persistent, appears not to be associated with other adverse outcomes

→ **Guidelines recommend against screening for or treating ASB**

When to Test and Treat

Pregnant Women

- Prevalence of ASB in pregnant women → 2-7%
- Rationale
 - Probable reduction in the subsequent risk of pyelonephritis
 - May reduce the risk of low birth weight
 - May reduce risk of pre term labor

→ **Guidelines recommend screening for and treating ASB**



When to Test and Treat: Geriatric Patients

- Incidence: 40-50% of LTC residents over 80yo
- Consider risk/benefit : Likely no reduction in in the risk of death or sepsis with treatment and acknowledgement of frequent ASE's
- Functional and/or cognitive impairment with bacteriuria and delirium and **without** local GU symptoms or systemic signs of infection → diagnostic challenge
- Functional and/or cognitive impairment with bacteriuria and **without** local GU symptoms or systemic signs of infection who experience a fall
 - “Bacteriuria is usually unrelated and simply a confounding factor.”

→ **Guidelines recommend observation and assess for other causes**

When to Test and Treat



Diabetic Patients:

- Antimicrobials may not reduce the risk of symptomatic urinary infection (including pyelonephritis) and again considering risk of ASE's
- An interesting point: prospective cohort studies also found that there were no between-group differences in the progression to diabetic complications and mortality.
 - Of note: recommendations for diabetic men are inferred from studies primarily enrolling women

→ **Guidelines recommend against screening for or treating ASB**

When to Test and Treat

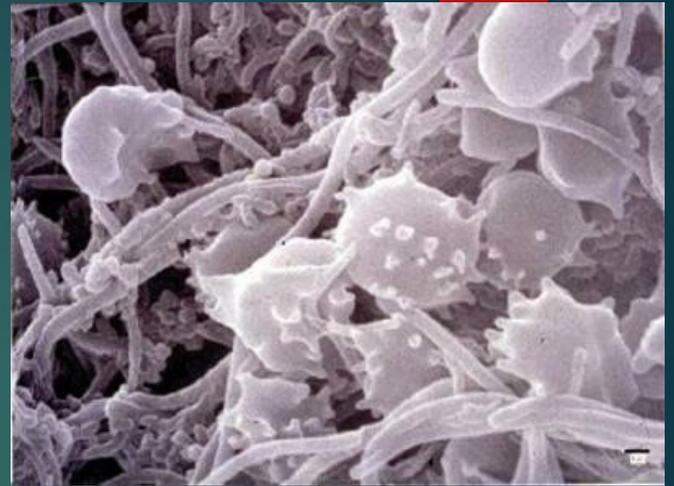
Indwelling urethral catheters:

- Short term (< 30 days)
- Chronic indwelling

Role of Biofilms:

- Risk/benefit - benefit to treating ASB is uncertain but there is high quality evidence of resulting harm with increased resistance

→ **Guidelines recommend against screening for or treating ASB**



What we are trying to avoid...

	Klebsiella oxytoca AUTOMATED SUSCEPTIBILITY (PHOENIX)		
Amikacin	<=4 ug/mL	Susceptible	
Amoxicillin/Clavulanic	16/8 ug/mL	Intermediate	
Ampicillin	> 16 ug/mL	Resistant	
Ampicillin/Sulbactam	> 16/8 ug/mL	Resistant	
Aztreonam	> 16 ug/mL	Resistant	
Cefazolin	> 32 ug/mL	Resistant	
Cefepime	> 16 ug/mL	Resistant	
Ceftazidime	> 16 ug/mL	Resistant	
Ceftriaxone	> 32 ug/mL	Resistant	
Cefuroxime	> 16 ug/mL	Resistant	
Ciprofloxacin	2 ug/mL	Resistant	
Ertapenem	<=0.125 ug/mL	Susceptible	
Gentamicin	> 8 ug/mL	Resistant	
Imipenem	0.5 ug/mL	Susceptible	
Meropenem	<=0.125 ug/mL	Susceptible	
Nitrofurantoin	<= 16 ug/mL	Susceptible	
Piperacillin/Tazobactam	16/4 ug/mL	Susceptible	
Tetracycline	> 8 ug/mL	Resistant	
Tobramycin	> 8 ug/mL	Resistant	
Trimethoprim/Sulfamethoxazole	> 2/38 ug/mL	Resistant	

Knowledge Test #3

24 yo female presents with 3d of dysuria, urgency, and frequency. She denies fevers or flank pain. No overt hematuria. Last treated for UTI one year ago with Ciprofloxacin 250mg PO BID x 3d with resolution of symptoms at that time. She has NKDA. Pregnancy test is neg.

VS: BP 112/74, T 97.8F, HR 84, R 14

UA: > 75 WBC/HPF, 0-3 RBC/HPF, + nitrite, Many bacteria, and Large Leukocyte Esterase

Urine Cx: > 100,000 CFU/mL E coli (Pan - S)

What is your drug & duration of choice for this patient?

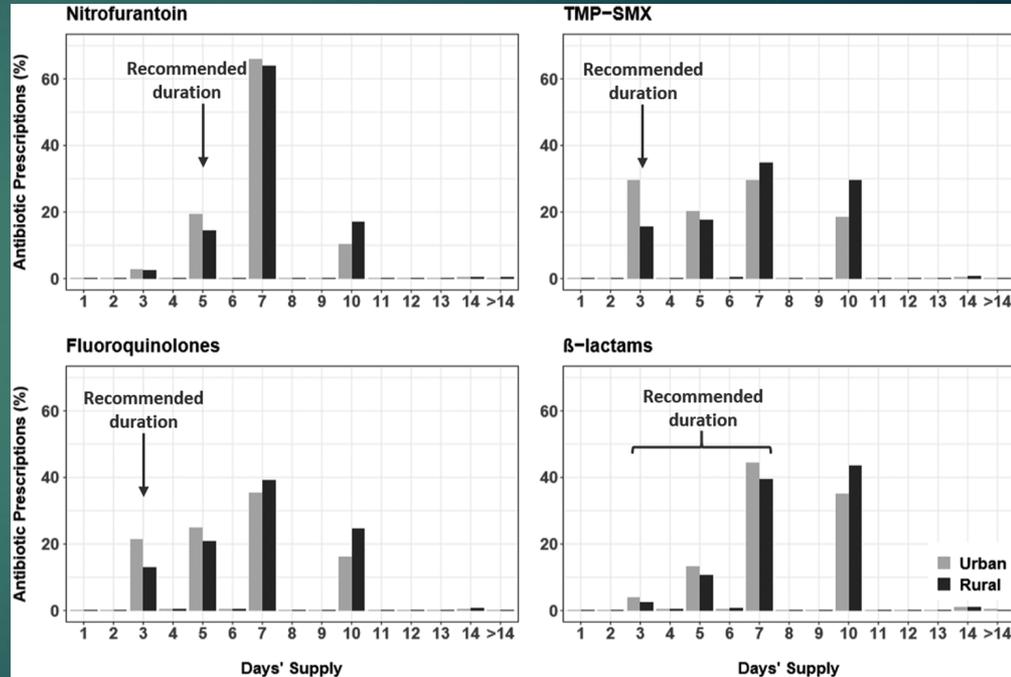
- A) Ciprofloxacin 250mg PO BID x 3 d
- B) TMP/SMX 1 PO DS BID x 3 d
- C) TMP/SMX 1 PO DS BID x 7 d
- D) Nitrofurantoin 100mg PO BID x 7d

UTI and Stewardship

Estimated 7 million office visits, 1 million ER visits, and 100,000 hospitalizations for UTI in the US annually

Associated annual cost: \$1.6 billion

2021 study of 670K women with uncomplicated UTI → 47% received inappropriate agent, 76.1% received inappropriate duration



UTI - Treatment Options

Antibiotic	Dosing	Duration	Clinical Cure	Bacterial Cure
Nitrofurantoin	100 mg BID	5 days	90%	92%
		7 days	93-95%	86%
TMP/SMX	1 DS BID	3 days	90-100%	91-100%
		7 days	86-95%	85-93%
Fosfomycin	3 gm x 1	1 day	83-95%	78-98%
Ciprofloxacin	250 mg BID	3 days	89-95%	88-92%
Levofloxacin	250 mg QD	3 days	-	83%
Cephalexin	250-500 mg 4x/day	5 days	91%	83%
Cefpodoxime	100 mg BID	3 days	98%	98%

Clinical Case

55 yo F smoker with poorly controlled insulin dependent diabetes with neuropathy (**recent A1c 10.2**) presented to ED with **bilateral foot ulcers** present for > 1 month. She attributes development of these ulcers to poor fitting shoes. The ulcers have enlarged in size, now with **foul smelling discharge**, and surrounding **erythema**. She denies fevers or chills.

Vital signs on presentation: Tmax **100.6 F** (38.1 C); HR **100**; BP 130-150/90's; RR 18

Physical exam:

- General appearance: alert, oriented, in no distress
- HEENT: moist mucous membranes
- CV: RRR
- Respiratory: CTAB
- Skin: **ulcerations to lateral/plantar portion of both great toes with surrounding erythema and foul smelling purulent appearing discharge. Erythema extending to base of first toes bilaterally. Wounds do not probe to bone bilaterally.**

Diagnostic Findings

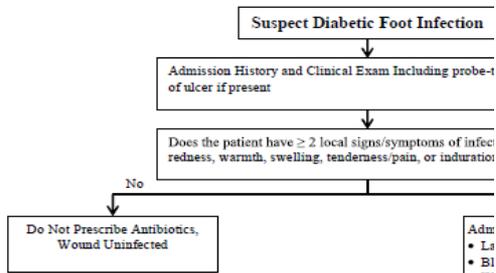
Pertinent lab values:

- WBC – **12.5; 89% neutrophils**
- Lactate 1
- ESR – **65** (normal range 0-30)
- CRP **150** (normal range 5-15)
- Cr 1.0 (baseline 1.0-1.2)
- Normal LFT's
- Blood cultures - no growth x two sets

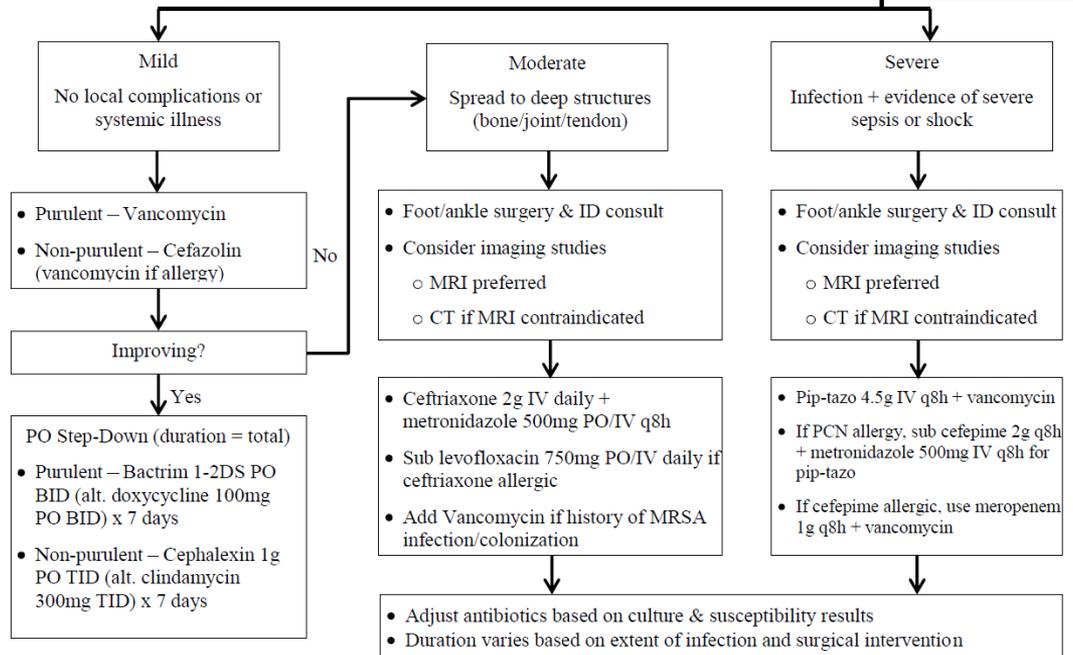
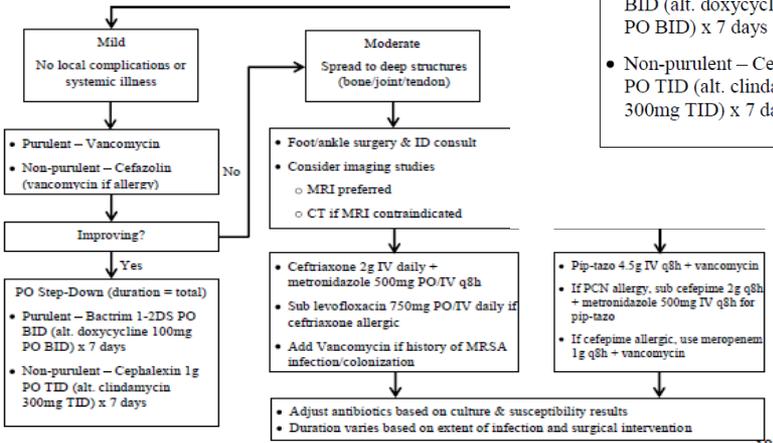
X-ray of bilateral feet demonstrated
no evidence of osteomyelitis.

Next steps?





Adm
• Ls
• Bl
• W
• B+
pp
an



Diabetic Foot Infections Algorithm - UCH

Case...

MRI findings demonstrate soft tissue abscesses surrounding bilateral first metatarsals with no evidence of extension to joints. **No evidence of osteomyelitis.**

Foot/ankle consulted- patient taken to OR for I&D of bilateral abscesses. Op report noted extension of infection into subcutaneous tissue but **did not appear to extend to tendons, joint or bone bilaterally.**

OR cx's obtained from soft tissue with growth of MRSA (S bactrim, doxycycline, clindamycin) and mixed anaerobes.

Case Discussion

What treatment course should be recommended for this patient?

- **Right drug(s):**
 - Target culture data
 - Look at susceptibility p
- **Right route/dose:**
 - Does this patient need
 - Are their antibiotic opt
 - bioavailability if giving
 - What is the appropriat
 - infection?
- **Right duration:**
 - What is the appropriat

CNS, Bone, and Urinary Penetration for Select Antimicrobial Agents				
Drug	CNS Uninflamed (%)	CNS Inflamed (%)	Bone	Urine
Beta-Lactams - Penicillins				
Penicillin G/V	Low	Moderate (30)	N/A	Excellent
Nafcillin	Low (1-2)	Moderate (20-30)	Moderate	Good
Ampicillin	Low (1.6)	Moderate (39)	Mod-Good	Good
Sulbactam	Low (7)	Low (10)	Mod-Good	Good
Amoxicillin	Low	Low (5.8)	Moderate	Excellent
Clavulanic Acid	Low (3.7)	Low (8.4)	Moderate	Excellent
Piperacillin / tazobactam ²	Low (3.7/10.6)	Moderate (32)	Moderate	Good
β-Lactams- Monobactam				
Aztreonam	Moderate	Moderate (13-18)	Moderate	Good
β-Lactams – Cephalosporins				
Cefazolin ²	Low	Low (9-10)	Moderate	Excellent
Cefotaxime	Low (9)	Moderate (17)	Moderate	Good
Cefoxitin ²	Low (0-9)	Good (41-50)	Moderate	Good
Ceftriaxone	Low (0.7-2)	Moderate (20-35)	Moderate	Good
Ceftazidime	Low (2-8)	Moderate (36-40)	Mod-Good	Excellent
Ceftazidime-Avibactam ¹	N/A	N/A	N/A	Excellent
Cefepime	Low (8-10)	Moderate (20-34)	Good	Good
Ceftolozane-Tazobactam ²	N/A	N/A	N/A	Excellent
Ceftaroline ²	Low (3)	Moderate (15)	N/A	Good
β-Lactams – Carbapenems				
Ertapenem ²	?	Low-Moderate	Moderate	Good
Meropenem	Moderate (5-25)	Good (39-75)	Moderate	Good
Imipenem/Cilastatin	Low	Moderate (14)	Low	Good
Fluoroquinolones				
Ciprofloxacin ²	Good (24-43)	Excellent (92)	Excellent	Excellent
Moxifloxacin ^{2,3}	Good (46)	Excellent (71-94)	Excellent	Low

Knowledge Test #4

Patient received 3 days of IV **Vancomycin and Zosyn** while inpatient and was clinically improving with resolution of fevers and leukocytosis.

ID team was consulted for antibiotic choice and duration for discharge.

What is the most appropriate drug choice and duration of therapy for this patient on discharge?

- A) Doxycycline for 5 additional days
- B) Clindamycin for 4 additional days
- C) Keflex for 7 additional days
- D) Linezolid + Flagyl for 10 additional days

Novel Agents for SSTI's: Long Acting Lipoglycopeptides

Dalbavancin

Indication: treatment of adults and peds w/ ABSSSI caused by select Gram-positive organisms

Coverage: MSSA, MRSA, Strep pyogenes, Strep agalactiae, Strep dysgalactiae, Strep anginosus group, E faecalis (Not VRE)

Standard Dosing: one time infusion of 1,500mg over 30 min; Half life 346 hrs

ASE's: nausea (5.5%), headache (4.7%) diarrhea (4.4%)

Monitoring: CBC with diff, CMP at baseline and 2 weeks later; monitor for infusion reaction during treatment

Oritavancin

Indication: treatment of adults w/ ABSSSI caused by select Gram-positive organisms

Coverage: MSSA, MRSA, Strep pyogenes, Strep agalactiae, Strep dysgalactiae, Strep anginosus group, E faecalis (Not VRE) **

Standard Dosing: one time infusion of 1,200mg over 3 hours; Half life 245 hrs

ASE's: (>3%): headache, nausea/vomiting, limb and SQ abscesses, and diarrhea

Monitoring: CBC with diff, CMP at baseline and 2 weeks later; monitor for infusion reaction; interaction with heparin/AC

Summary Slide

- Inappropriate antibiotic use leads to increased rates of resistance and adverse effects but does not result in improvement of clinical outcomes
- Most common scenarios where antibiotics are misused include:
 - Respiratory tract infections (including PNA)
 - Urinary infections, including asymptomatic bacteriuria
<https://www.idsociety.org/practice-guideline/asymptomatic-bacteriuria/>
 - Skin and soft tissue infections
- Good stewardship practices include using the **right drug(s)**, with the **right route/dose**, for the **right duration**
 - Many common infections can be treated with <7 days of antibiotics
- Always use your resources!

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Thank you!

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