# Choosing Antibiotics Wisely

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# disclosure

▶ No conflict of interest

#### objectives

After this session, participants will be able to:

- Describe the role and necessity of antimicrobial stewardship programs
- 2. Identify interventions that are employed by antimicrobial stewardship programs to improve the quality of care
- 3. Implement principles of antimicrobial stewardship and best practice in their own prescription practices and help to educate others



#### Caveat

- Infectious diseases
  - Evidence based medicine vs expert opinion
  - 2011 analysis >50% of IDSA recommendations were based on level III evidence
- Local microbiology is important
- Affiliated infectious diseases units, infection prevention and control units, and antimicrobial stewardship programs should be your primary resource

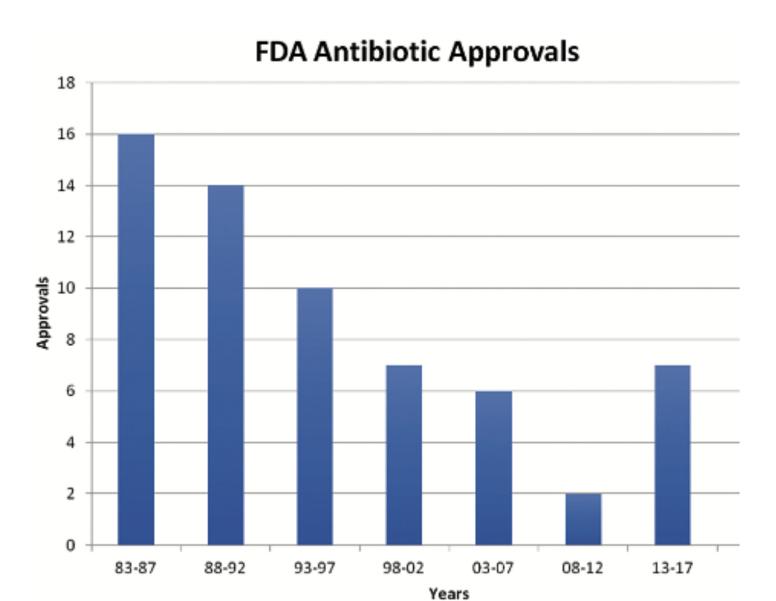
# Antibiotics in FDA Approval Pipelines

- Meropenem-vaborbactam
- Delafloxacin
- Lefamulin
- Fosfomycin IV
- Plazomicin

- Cefiderocol
- Omadacycline
- Iclaprim
- Relebactam(-imipenem)
- Eravacycline



Ten new **ANTIBIOTICS** by 2020





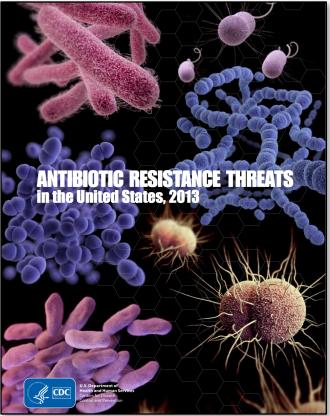


#### NATIONAL STRATEGY FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

Vision: The United States will work domestically and internationally to prevent, detect, and control illness and death related to infections caused by antibiotic-resistant bacteria by implementing measures to mitigate the emergence and spread of antibiotic resistance and ensuring the continued availability of therapeutics for the treatment of bacterial infections.

September 2014











## Antibiotic Stewardship

- "activity that includes appropriate selection, dosing, route, and duration of antimicrobial therapy"
- "optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms, and the emergence of resistance"

#### Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship

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#### **EXECUTIVE SUMMARY**

This document presents guidelines for developing institutional programs to enhance antimicrobial stewardship, an activity that includes appropriate selection, dosing, route, and duration of antimicrobial therapy. The multifaceted nature of antimicrobial stewardship has led to collaborative review and support of these recommendations by the following organizations: American Academy of Pediatrics, American Society of Health-System Pharmacists, Infectious Diseases Society for Obstetrics and Gynecology, Pediatric Infectious Diseases Society, Society for Hospital Medicine, and Society of Infectious Diseases Pharmacists. The primary goal of antimicrobial stewardship is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms (such as Clostridium difficile), and the emergence of resistance. Thus, the appropriate use of antimicrobials is an essential part of patient safety and deserves careful oversight and guidance. Given the association between antimicrobial use and the selection of resistant pathogens, the frequency of inappropriate antimicrobial use is often used as a surrogate marker for the avoidable impact on antimicrobial resistance. The combination of effective antimicrobial stewardship with a comprehensive infection control program has been shown to limit the emergence and transmission of antimicrobial-resistant bacteria. A secondary goal of antimicrobial stewardship is to reduce health care costs without adversely impacting quality of care.

These guidelines focus on the development of effective hospital-based stewardship programs and do not include specific outpatient recommendations. Although judicious use of antimicrobials is important in outpatient clinics and long-term care facilities, there are very few data regarding effective interventions, and it is unclear which interventions are most responsible for improvement in these settings.

The population targeted by these guidelines includes all patients in acute care hospitals. Most of the evidence supporting the recommendations in these guidelines is derived from studies of interventions to improve antimicrobial use for hospitalized adults. Many of these studies have focused on adults in intensive care units. Only a handful of studies have focused on hospitalized newborns, children, and adolescents. Few studies have included substantial populations of severely immunocompromised patients, such as patients undergoing

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Received 3 October 2006; accepted 4 October 2006; electronically published 13 December 2006.

These guidelines were developed and issued on behalf of the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America.

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#### Antimicrobial Stewardship



- Accreditation Canada recognizes the overuse of antimicrobials and risks associated with this
- Required Organization Practice (ROP)

"A successful antimicrobial stewardship program requires an inter-disciplinary approach, with collaboration between the antimicrobial stewardship team, pharmacy, and hospital infection control. The involvement and support of hospital administrators, medical staff leadership, and health care providers is essential."

#### Paradigm shifts for stewardship

Comprehensive part of battling anti-microbial resistance

Overall quality of care, ROP of Accreditation Canada (Performance tied to CEO rewards in US healthcare systems)

#### ASP – the nutshell version

- Correct Drug
- Correct Dose
- Correct Route
- Correct Diagnosis
- ► TDM (vancomycin, aminoglycosides, voriconazole, posaconazole)
- Education

#### Antimicrobial stewardship program

- Preauthorization
- Prospective audit and Feedback
- Clinical practice guidelines
- Interventions targeting syndromes or certain antimicrobials
- Interventions designed to reduce antibiotic usage with strong association with CDI

## Antimicrobial stewardship program

- Strategies to encourage prescriber led review of appropriateness of antibiotic regimens (antibiotics time-outs, stop orders)
- Computerized decision support
- PK monitoring
- Alternative dosing of vancomycin and beta-lactams using PK/PD data to improve outcomes and decrease costs (i.e meropenem q6h vs q8h)

#### Antimicrobial stewardship program

- IV to PO switch where indicated
- Allergy consultation to improve safe use of guideline recommended betalactams
- Reduction of antibiotics to shortest effective duration
- Stratified antibiogram, Cascading antibiogram
- Use of rapid viral testing for respiratory pathogens
- Use of serial PCT in ICU patients
- ASP support in LTC and end of life care

#### Measures of Utilization

- DDD Daily Defined Dose
  - Grams of antibiotic are normalized against a WHO standard that has been agreed to represent average usual use of an antibiotic.
  - ie 1 DDD for cephazolin = 3g / day if you prescribe Ancef 2g IV q8h (6g / day), you are using 2 DDDs
  - Shortcomings: disease severity, obesity, renal insufficiency/dialysis, pediatrics
- DOT Days of Therapy
  - Each antibiotic given on a given day contributes 1 DOT
- LOT Length of Therapy
  - A single LOT is contributed for a day where at least 1 antibiotic has been administered
- DDD / 1000 patient-days (available readily in JGH pharmacy IS)
- DOT / 1000 patient-days (CDC benchmarks)

# Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and *Clostridium difficile* infection: a systematic review and meta-analysis



David Baur\*, Beryl Primrose Gladstone\*, Francesco Burkert, Elena Carrara, Federico Foschi, Stefanie Döbele, Evelina Tacconelli

#### Summary

Background Antibiotic stewardship programmes have been shown to reduce antibiotic use and hospital costs. We aimed to evaluate evidence of the effect of antibiotic stewardship on the incidence of infections and colonisation with antibiotic-resistant bacteria.

Methods For this systematic review and meta-analysis, we searched PubMed, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and Web of Science for studies published from Jan 1, 1960, to May 31, 2016, that analysed the effect of antibiotic stewardship programmes on the incidence of infection and

#### Lancet Infect Dis 2017

Published Online June 16, 2017 http://dx.doi.org/10.1016/ S1473-3099(17)30325-0

See Online/Comment http://dx.doi.org/10.1016/ 51473-3099(17)30344-4

	Number of studies	Incidence ratio (95% CI)
Study setting		
Intensive care unit	10 —	0.77 (0.66-0.89)
Medical ward	27 —	0.78 (0.66-0.91)
Surgical ward	5	0.76 (0.46-1.25)
Haematology-oncology ward	3	0.41 (0.20-0.85)
Co-implementation of ICMs		
ASP alone	23 —	0.81 (0.67-0.97)
ASP + ICMs	9 —	0.69 (0.54-0.88)
ASP + hand-hygiene intervention	5 —	0.34 (0.21-0.54)
Type of intervention		
Antibiotic restriction	15 —	0.77 (0.67-0.89)
Audits/feedback	19 ——	0.66 (0.52-0.83)
Antibiotic cycling	3 —	0.49 (0.34-0.72)
Year of study		
1980-2000	5	0.90 (0.60-1.36)
2001-05	10 —	0.79 (0.69-0.90)
2006-13	17 —	0.68 (0.49-0.95)
Infection and/or colonisation		
Infection and colonisation	8	0.91 (0.60-1.37)
Infection	21 —	0.75 (0.66-0.85)
Colonisation	3	0.72 (0.41-1.25)
Study design		
Interrupted time-series studies	6	1.20 (0.97-1.50)
Cohort studies	7	0.79 (0.61-1.02)
Before-after studies	18 —	0.66 (0.54-0.81)
	0 0.5 1.0 1.5	2.0
	ASP effective ASP not effective	ve .

Figure 5: Summary forest plot of the incidence ratios for studies investigating the effect of ASPs on antibiotic resistance, according to study characteristics

ICM=infection control measure. ASP=antibiotic stewardship programme.

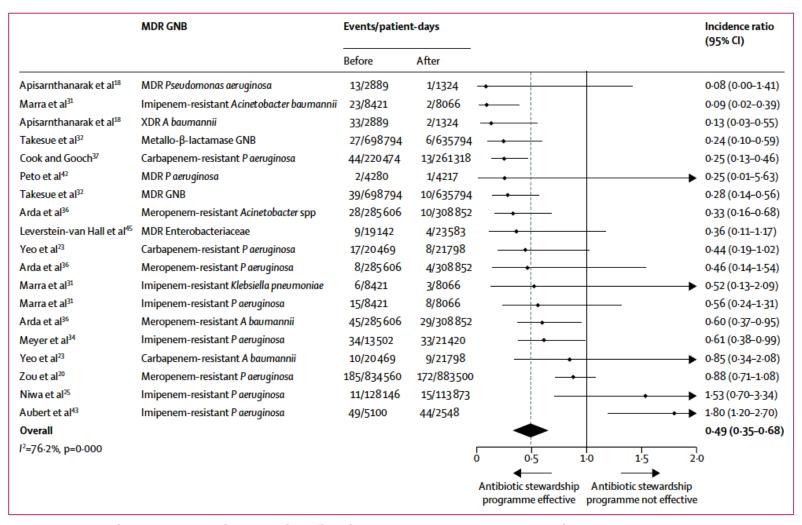


Figure 2: Forest plot of the incidence ratios for studies of the effect of antibiotic stewardship on the incidence of MDR GNB GNB=Gram-negative bacteria. MDR=multidrug-resistant. XDR=extensively drug-resistant.

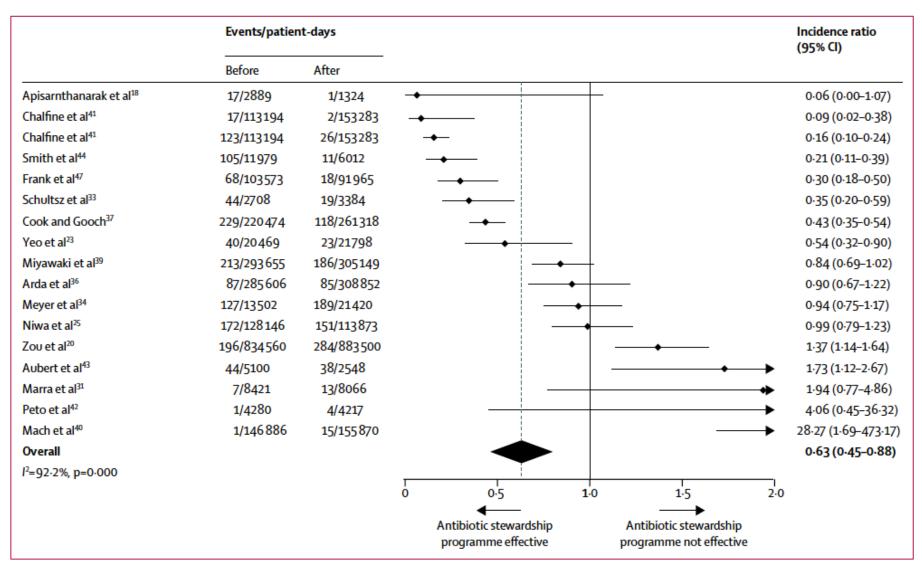


Figure 3: Forest plot of the incidence ratios for studies of the effect of antibiotic stewardship on the incidence of meticillin-resistant Staphylococcus aureus

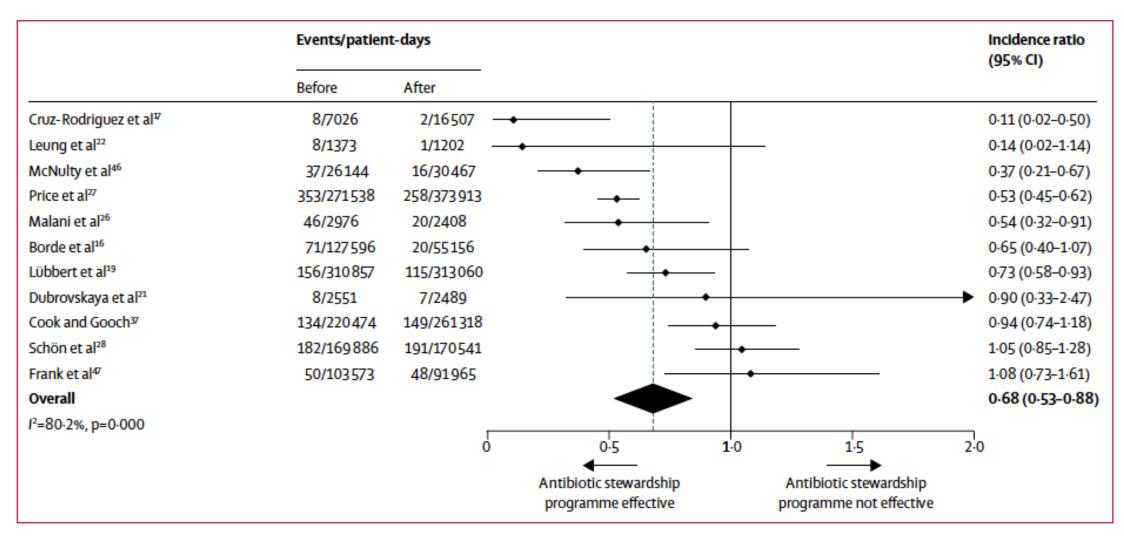


Figure 4: Forest plot of the incidence ratios for studies of the effect of antibiotic stewardship on the incidence of Clostridium difficile infections



#### Restrict Antibiotics to **Bacterial** Infection

- Don't prescribe antibiotics in vaccinated children more than 6 months old and adults in whom you suspect acute otitis media, unless there is either a perforated tympanic membrane with purulent discharge or a bulging tympanic membrane with one of the three following criteria:
  - Fever (≥39°C)
  - Moderately or severely ill
  - Significant symptoms lasting > 48 hours
- Don't routinely prescribe antibiotics unless the patient's modified <u>Centor</u> score is ≥ 2 AND throat swab culture (or rapid antigen test if available) confirms presence of Group A Streptococcus.

#### Restrict Antibiotics to **Bacterial** Infection

- Don't prescribe antibiotics for bronchitis/asthma/bronchiolitis exacerbations.
- Don't prescribe antibiotics for ILI unless there is clear evidence of secondary bacterial infection (see the recommendations for otitis media, pharyngitis, sinusitis, pneumonia).
- Don't prescribe antibiotics unless there is clear evidence of secondary bacterial infection (see the recommendations for otitis media, pharyngitis, sinusitis, pneumonia).
- Don't prescribe antibiotics for sinusitis unless symptoms have persisted for greater than 7-10 days without improvement.

The symptoms you	presented with today suggest a VIRAL infection.
	Tract Infection (Common Cold) : Lasts 7-14 days
•	/3 ("Sore Throat") : Lasts 3-7 days, up to ≤10 days
	Chest Cold" (Cough): Lasts 7-21 days
	nus Infection") : Lasts 7-14 days
	have not been prescribed antibiotics because
antibiotics are Antibiotics can cause	e not effective in treating viral infections. e side effects (e.g. diarrhea, yeast infections) and may cause as severe diarrhea, allergic reactions, kidney or liver injury.
When you have a viral	l infection, it is very important to get plenty of rest and
give your body time to	
	these instructions, you should feel better soon :
→ Rest as m → Drink pler	nuch as possible
	ur hands frequently
	r-the-counter medication, as advised :
Acetaminophen (e.	.g. Tylenol®) for fever and aches
Ibuprofen (e.g. Adv	vil®) for fever and aches
Naproxen (e.g. Ale	eve®) for fever and aches
Lozenge (cough ca	andy) for sore throat
	Salinex®) for nasal congestion
Other :	
	decongestant if Salinex® does not work, for short-term use only!)
	to your provider if:
	s do not improve in day(s), or worsen at any time lop persistent fever (above 38°C, or as directed)
»→ Other:	
Prescriber	





This "Viral Prescription Pad" has been adapted from the RQHR Antimicrobial Stewardship Program www.rqhealth.ca/antimicrobialstewardship, and is available in other languages. http://www.rxfiles.ca/rxfiles/uploads/documents/ABX-Viral-Prescription-Pad-Languanges.pdf

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

#### Restrict Antibiotics to **Bacterial** Infection

- Don't prescribe antibiotics for pneumonia unless there is objective evidence.
- Don't routinely prescribe antibiotics for exacerbations of Chronic Obstructive Pulmonary Disease <u>unless there is clear increase in</u> <u>sputum purulence with either increase in sputum volume and/or</u> <u>increased dyspnea</u>

# R DELAYED PRESCRIPTION

#### **About Your Delayed Prescription**

WAIT. Don't fill your prescription just yet. Your health care provider believes your illness may resolve on its own. Follow the steps below to get better.

First, continue to monitor your symptoms over the next few days and try the following remedies to help you feel better:

- · Get lots of rest.
- Drink plenty of water.
- For a sore throat: ice chips, throat lozenges or spray, or gargle with salt water.
- For a stuffy nose: saline nasal spray or drops.
- For fever and pain relief: acetaminophen or ibuprofen.

Other:
--------

Wash your hands often to avoid spreading infections.

If you don't feel better in \_\_\_\_\_ days, go ahead and fill your prescription at the pharmacy.

If you feel better, you do not need the antibiotic and the prescription can be thrown out.

If things get worse, please contact your health care provider.

Antibiotics should only be taken when medically necessary. Unwanted side effects like diarrhea and vomiting can occur, along with destruction of your body's good bacteria that can leave you more susceptible to infections.

To learn more, visit www.choosingwiselycanada.org/antibiotics





#### Restrict Antibiotics to Bacterial infection

- Don't prescribe antibiotics after incision and drainage of uncomplicated skin abscesses unless extensive cellulitis exists. | <u>Emergency medicine #5</u>
- Don't prescribe antibiotics for asymptomatic bacteriuria (ASB) in non-pregnant patients. | <u>Hospital medicine #2</u>
- Don't order peri-operative antibiotics beyond a 24-hour post-operative period for non-complicated instrumented cases in patients who are not at high risk for infection or wound contamination. Administration of a single pre-operative dose for spine cases without instrumentation is adequate. | Spine #5
- Don't use antimicrobials to treat bacteriuria in older adults unless specific urinary tract symptoms are present. | Geriatrics #1
- Don't recommend antimicrobials to treat bacteriuria in older adults unless specific urinary tract symptoms are present. | Nursing #8

#### Restrict Antibiotics to Bacterial infection

- Don't use antimicrobials to treat asymptomatic bacteriuria in the elderly. | <u>Urology #4</u>
- Do not treat asymptomatic urinary tract infections in catheterized patients. | <u>Physical medicine and rehabilitation #1</u>
- Don't routinely prescribe intravenous forms of highly bioavailable antimicrobial agents for patients who can reliably take and absorb oral medications. | <u>Infectious disease #1</u>
- Don't prescribe alternate second-line antimicrobials to patients reporting nonsevere reactions to penicillin when beta-lactams are the recommended first-line therapy. | <u>Infectious disease #2</u>

# Case – Antibiotic interactions, AE profile

#### 75F

AF, HTN, cystocele left her medication list at home, DSQ is down

Concerned about dysuria and frequency for the past 3 days
No systemic symptoms

UA -nit +LE

Rx ciprofloxacin 250mg PO bid x 3 days

# DO TAKE A FULL MEDICATION HISTORY, BE AWARE OF INTERACTIONS, ANTAGONISM AND ADVERSE EFFECT PROFILES

- Important interactions may occur
- → ↑INR
  - ▶ Warfarin ↔ FQ
  - Warfarin ↔ macrolides
  - ▶ Warfarin ↔ SXT-TMP
- QTc prolongation, risk of malignant arrhythmia
  - Especially elderly women
  - Especially if slower HR

#### case – weight-based dosing

36M body builder

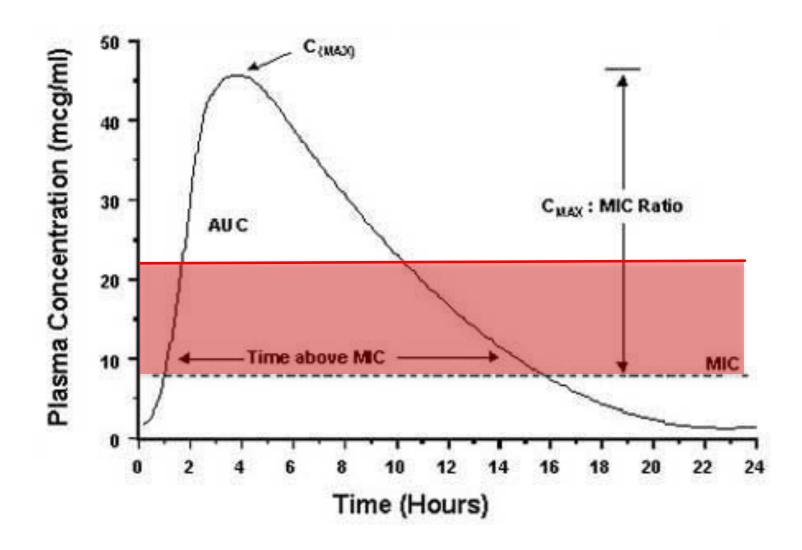
Episodic constipation

3 days of fever, LLQ pain Appears unwell on exam with LLQ palpation tenderness, rebound, and guarding

Rx amoxicillin clavulanic acid 500mg PO tid

# DO CONSIDER PATIENT'S BMI, IBW, ABW, AND MUSCLE MASS

- Under dosing risks treatment failure and selection of resistant mutant micro-organisms
- Pitfall of start and stop therapies
- Pitfall of prophylactic therapies



#### case – tissue penetration

#### 25F

No PMH

bonafide allergies to penicillin, and ciprofloxacin

4 days of dysuria and frequency

UA +nit +LE

Rx clindamycin 300mg PO tid x7 days

# DO CONSIDER TISSUE PENETRATION OF THE ANTIMICROBIAL, LOCAL TISSUE PHYSIOLOGY AND CHEMISTRY

- does it penetrate/concentrate into the urine?
- Can it penetrate all zones of the prostate?
- Can it cross the blood brain barrier?
- Can it penetrate bone / joints / lungs?
- Does surfactant interact with the antibiotics?
- Does this medication concentrate intracellularly?

#### case – oral bioavailability

46M

smoker, dyslipidemia, HTN

1-week cough, rusty sputum, left chest pain with pleuritic component.

O/E appears unwell T38.4C. Decreased air entry left lung field, with rales audible on inspiration.

CXR showing left lung lobar consolidation CBC, chemistry, blood cultures drawn.

Rx amoxicillin 1g PO bid

#### DO CONSIDER BIOAVAILABILITY OF ORAL ANTIBACTERIAL AGENTS

- When the patient can take PO medication, and the gut is absorbing reliably, certain medications achieve levels that are equivalent to receiving intravenous doses.
  - Fluoroquinolones i.e ciprofloxacin, levofloxacin, moxifloxacin
  - ► Macrolides ie azithromycin
  - clindamycin
  - trimethoprim-sulfamethoxazole
  - doxycycline

#### case – duration of therapy

#### 83F

T2DM, CAD, dyslipidemia

Presented in septic shock and jaundiced after acute abdominal pain. Started on broad spectrum antibiotics. ERCP demonstrated obstructing cholelithiasis, papillotomy and restoration of biliary patency. Blood cultures grow *Klebsiella pneumoniae*.

Rx Pip-Tazo 3.375g IV q6h x 14d ordered

#### DO CONSIDER THE DURATION OF THERAPY

- Magic numbers are going out, especially for cellulitis and pneumonia
- Shorter and shorter therapies are in
  - 7-d vs 14-d for uncomplicated Gram negative bloodstream infection
- ?Earlier stepdown

#### Forest plot depicting the risk ratios of 90-day mortality among patients receiving antibiotic treatment for ≤10 days versus >10 days.

	Short-co	urse	Long.co	urse		Risk Ratio		Risk Ratio
Study or Subgroup	<b>Events</b>	Total	<b>Events</b>	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% CI
Nelson 2017	8	91	7	199	8.8%	2.50 [0.93, 6.68]	2017	7
Yahav 2018	36	306	32	298	65.2%	1.10 [0.70, 1.72]	2018	8 —
Giannella 2018	11	426	13	430	26.0%	0.85 [0.39, 1.89]	2018	8
Total (95% CI)		823		927	100.0%	1.16 [0.81, 1.66]		•
Total events	55		52					
Heterogeneity: Chi <sup>2</sup> = 2.98, df = 2 (P = 0.23); I <sup>2</sup> = 33%								04 02 05 4 2 5 40
Test for overall effect	Z = 0.80 (R)	P = 0.43	)					0.1 0.2 0.5 1 2 5 10 Against short-course Against long-course

#### Forest plot depicting the risk ratios of clinical cure of patients receiving antibiotic treatment for ≤10 days versus >10 days.

	Short-co	urse	Long-co	urse		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% CI
Mercuro 2017	45	51	150	173	16.8%	1.02 [0.91, 1.14]	2017	<u>+</u>
Giannella 2018	344	426	341	430	83.2%	1.02 [0.95, 1.09]	2018	
Total (95% CI)		477		603	100.0%	1.02 [0.96, 1.08]		<b>•</b>
Total events	389		491					
Heterogeneity: Chi <sup>2</sup> = Test for overall effect:	The state of the s			)%				0.1 0.2 0.5 1 2 5 Favours short-course Favours long-course

Giannoula S. Tansarli et al. Antimicrob. Agents Chemother. 2019; doi:10.1128/AAC.02495-18



# Forest plot depicting the risk ratios of relapse of patients receiving antibiotic treatment for ≤10 days versus >10 days.

	Short-co	urse	Long-co	urse		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% CI
1.6.1 90-day								
Nelson 2017	6	91	15	199	20.7%	0.87 [0.35, 2.18]	2017	
Yahav 2018	8	306	8	298	17.8%	0.97 [0.37, 2.56]		
Giannella 2018 Subtotal (95% CI)	23	426 823	19	430 927	41.6% <b>80.2</b> %	1.22 [0.68, 2.21] 1.08 [0.69, 1.67]	2018	
Total events	37		42					
Heterogeneity: Chi <sup>2</sup> = 0.42 Test for overall effect: Z =			); l² = 0%					
1.6.2 30-day								
Chotiprasitsakul 2018 Subtotal (95% CI)	5	385 385	9	385 <b>385</b>	19.8% <b>19.8</b> %	0.56 [0.19, 1.64] <b>0.56 [0.19, 1.64]</b>	2018	
Total events	5		9					
Heterogeneity: Not applica	able							
Test for overall effect: Z =		0.29)						
Total (95% CI)		1208		1312	100.0%	0.97 [0.65, 1.46]		
Total events	42		51					
Heterogeneity: Chi <sup>2</sup> = 1.65	5, df = 3 (F)	= 0.65	); $I^2 = 0\%$				1	
Test for overall effect: Z=								0.1 0.2 0.5 1 2 5
Test for subgroup differen	nces: Chi²	= 1.23.	df=1 (P:	= 0.27).	I2 = 18.69	6		Against short-course Against long-course

Giannoula S. Tansarli et al. Antimicrob. Agents Chemother. 2019; doi:10.1128/AAC.02495-18



# case – de-labeling beta-lactam allergies

#### 52M

Hx of cellulitis left leg, eczema Topical corticosteroid Allergy to penicillin → rash.

2 day history of ascending erythema, swelling, pain in right leg. Fever.

Rx clindamycin 450mg PO tid

# DO HAVE A LOW THRESHOLD FOR CONSULTATION WITH A CLINICAL ALLERGIST TO RESOLVE BETA-LACTAM ALLERGY

- Patients should be provided the most narrow spectrum and most appropriate antibiotic
- At a patient's first encounter with a physician, when a penicillin allergy is described, a referral should be offered
- Many beta lactams can still be used safely in the context of a penicillin allergy, dependent on the reaction and the setting

#### Call to Action

- The next time you prescribe and antimicrobial or assess the need for an antibiotic, ask yourself:
  - 1. What am I treating? Is the (working) diagnosis established?
  - 2. Am I initiating appropriate antibiotics as per (local) empiric guidelines? Or, treatment in response to a culture result?
  - 3. Is there an alternative, more appropriate/targeted antibiotic? ... Or, no antibiotic necessary at all.
  - 4. How long should I treat?