Antimicrobial Stewardship: Prima non Nocere!

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Conflict of Interest Disclosure

I have no conflicts and nothing to disclose

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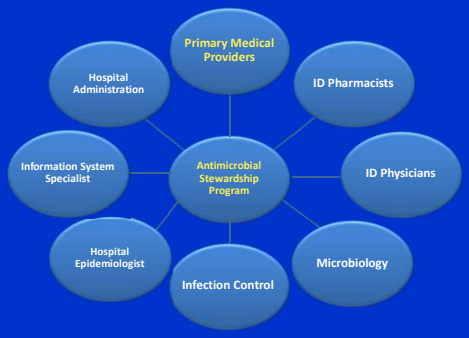
Objectives

- Describe antimicrobial stewardship and it's core elements
- Recognize the importance of antimicrobial stewardship and identify the consequences of improper antibiotic use
- Identify key ways in which clinicians can optimize antimicrobial use

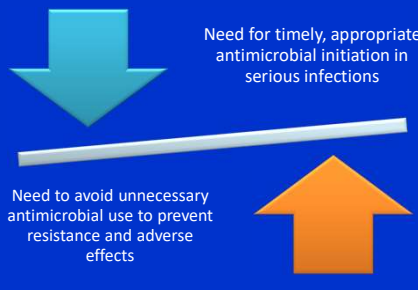
What is Antimicrobial Stewardship?

- Multidisciplinary approach optimizing appropriate antimicrobial selection (drug), dosing, and duration
- Minimize unintended consequences

Multidisciplinary Approach

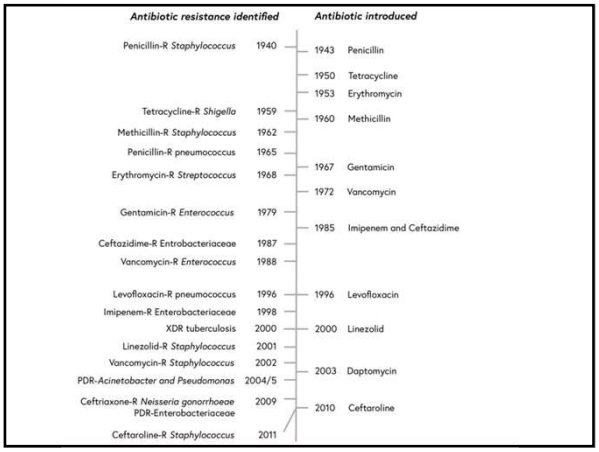


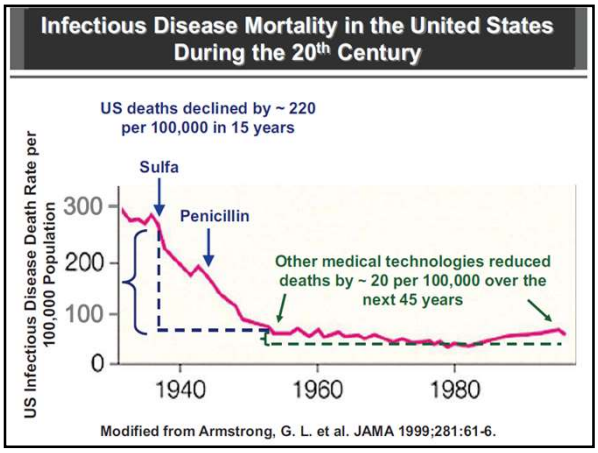
Dellit TH, et al. Clin Infect Dis. 2007;44:159–77.



ASP - National Priority

- 2014 – CDC recommended that all acute care hospitals implement an Antimicrobial Stewardship Program (ASP)
- June 2016 – Centers for Medicare and Medicaid Services (CMS) released a proposed rule change to require hospitals to implement ASPs, enhancements to infection control programs, and greater surveillance activities with ASP in order to participate in Medicare and Medicaid.
- July 2016 – The Joint Commission (TJC) approves new antimicrobial stewardship standards for all hospitals, critical care hospitals and nursing facilities.





Antibiotics
A Double Edged Sword

PROS

- Antibiotics appropriately ***selected*** and ***dosed***, ***given early, may be life saving***
  - **IF *host defenses are adequate***
  - **IF *infection unrelated to an abscess or obstruction***
  - **IF *infection not device associated***

Antibiotics
A Double Edged Sword

CONS

- **Antibiotic side effects**
  - Phlebitis
  - Hepatotoxity
  - Nephrotoxicity
  - Diarrhea (non-C. difficle & C. difficile)
  - Drug fever
  - Drug rash
  - Seizures
- **Antibiotic *drug-drug interactions***
- **Acquired antibiotic resistance (MDROs)**

C. difficile Infection (CDI)

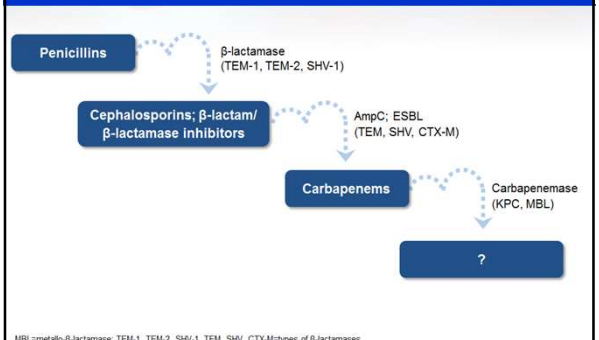
- Antibiotic exposure is the single most important risk factor for the development of CDI
- Patients who receive broad-spectrum antibiotics during hospitalization are 2.9 times more likely to develop CDI

United States Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2013. URL: http://www.cdc.gov/drugresistance/threat-report-2013/ [Accessed 2014 April 18]
Fridkin S, et al. Morbidity and Mortality Weekly Report. United States Center for Disease Control and Prevention. 2014;63(09):194-200.

Antibiotics May be Misused

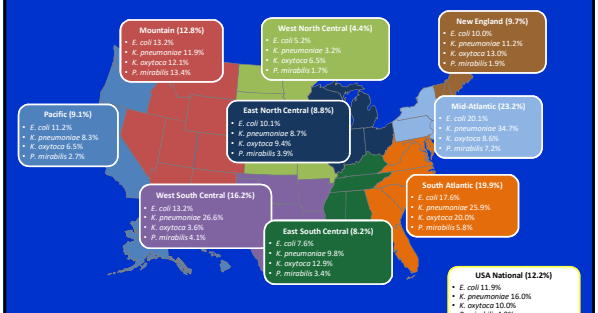
- Given when they are not needed
- Continued when they are no longer necessary
- Given at the wrong dose
- Broad spectrum used to treat very susceptible bacteria
- The wrong antibiotic is given to treat an infection
  - Inappropriate for site, nonsusceptible at site, tissue penetration problem

Development of Antibiotics in Response to Resistance Due to β-Lactamases

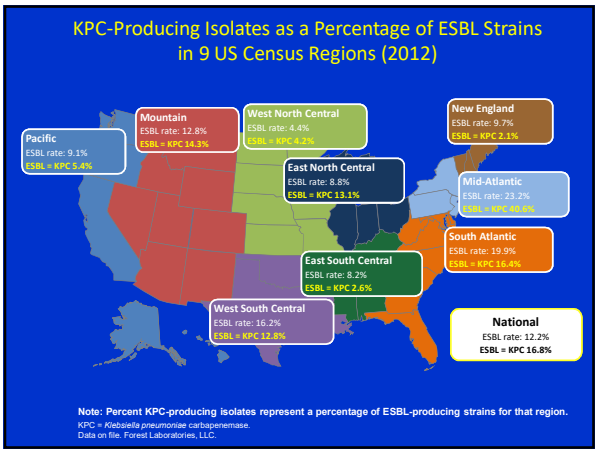


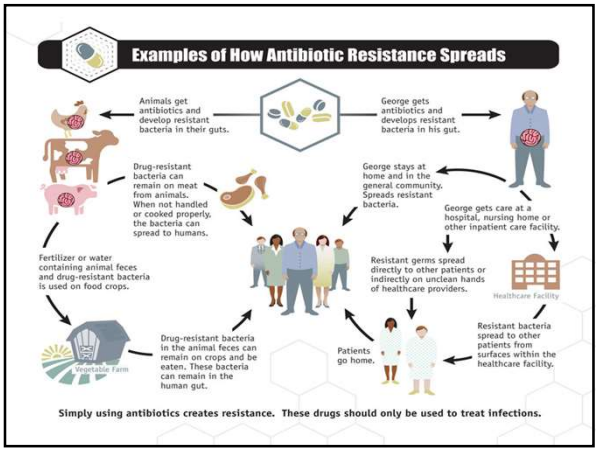
MBL=metallo-β-lactamase; TEM-1, TEM-2, SHV-1, TEM, SHV, CTX-M=types of β-lactamases.
Burgess DS, et al. *Am J Health-Syst Pharm*. 2008;65(suppl 2):S4-S15.

Percentage of ESBLs among Enterobacteriaceae Isolates Across 9 US Census Regions (2012)



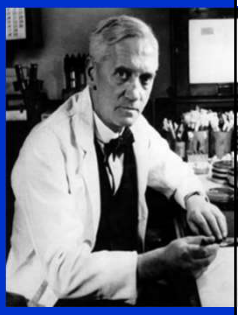
*KPC-producing *K. pneumoniae*, *E. coli*, and *K. oxytoca*.
Data on file. Forest Laboratories, LLC.



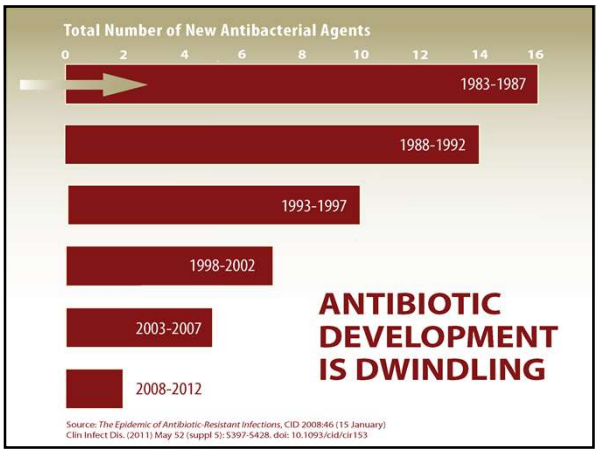


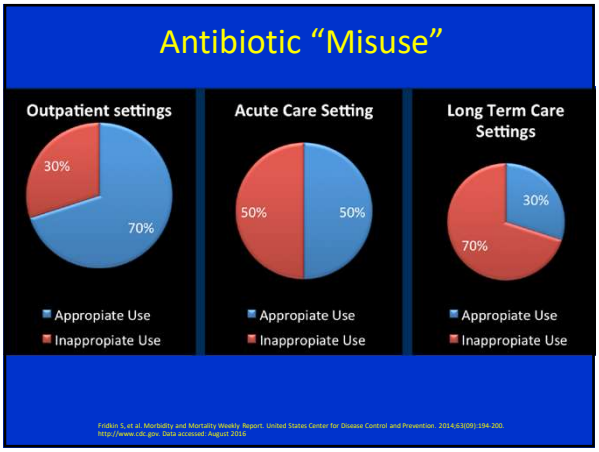
Alexander Fleming - 1945

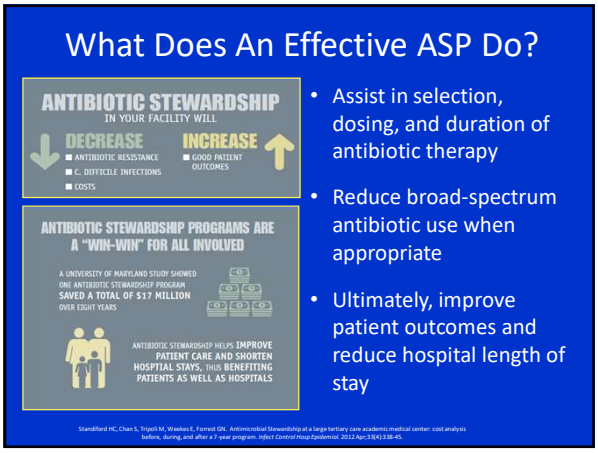
"The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out… In such cases the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted."



Penicillin Finder Assays its Future. New York Times. June 26, 1945 :21







- Assist in selection, dosing, and duration of antibiotic therapy
- Reduce broad-spectrum antibiotic use when appropriate
- Ultimately, improve patient outcomes and reduce hospital length of stay

CDC Core Elements of ASP

- **Leadership Commitment:** Dedicating necessary human, financial and information technology resources
- **Accountability:** Appointing a single leader responsible for program outcomes
- **Drug Expertise:** Appointing a single pharmacist leader responsible for working to improve antibiotic use
- **Action:** Implementing at least one recommended action, i.e. "antibiotic time out" after 48 hours

Clinical Infectious Diseases

MAJOR ARTICLE

Essential Resources and Strategies for Antibiotic Stewardship Programs in the Acute Care Setting

Sarah B. Doernberg,[1] Lilian M. Abbo,[2] Steven D. Burdette,[3] Neil O. Fishman,[4] Edward L. Goodman,[5] Gary R. Kravitz,[6] James E. Leggett,[7] Rebekah W. Moehring,[8] Jason G. Newland,[9] Philip A. Robinson,[10] Emily S. Spivak,[11] Pranita D. Tamma,[12] and Henry F. Chambers[1]

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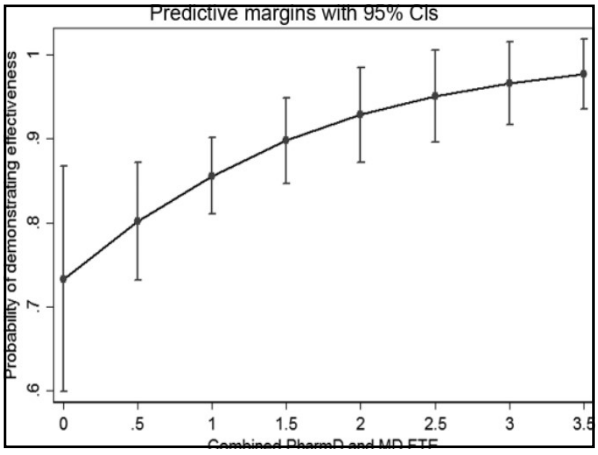
Table 6. Minimal Full-time Equivalent Support Recommended by Bed Size

Variable	Bed Size			
	100–300	301–500	501–1000	>1000
Pharmacist	1.0	1.2	2.0	3.0
Physician	0.4	0.4	0.6	1.0
Total	1.4	1.6	2.6	4.0

For hospitals with <100 beds, there were limited data to make recommendations.

Clin Infect Dis. 2018 Sep 28;67(8):1168-1174. doi: 10.1093/cid/ciy255



CDC Core Elements of ASP

- **Tracking:** Monitoring antibiotic prescribing and resistance patterns
- **Reporting:** Regular reporting information on antibiotic use and resistance to doctors, nurses and relevant staff
- **Education:** Educating clinicians about resistance and optimal prescribing

ASP – Not Just an Inpatient Issue

- Inpatient is important and is typically the most developed / has most resources
- Long term-care facilities
- Dialysis facilities

ASP – Not Just an Inpatient Issue

- Outpatient settings:
  - Emergency departments
  - Walk-in clinics/Urgent care centers
  - Ambulatory Surgery Centers (ASCs)
  - Physician offices
  - Outpatient pharmacies
- Non-human antibiotic use (livestock, etc)

BlueCross BlueShield

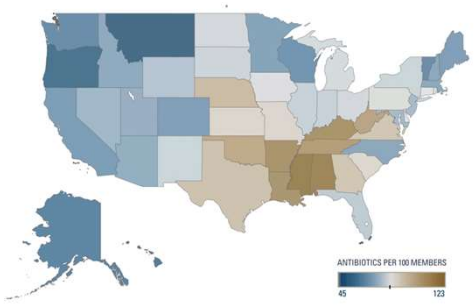
bhi Blue Health Intelligence

THE HEALTH OF AMERICA® REPORT

ANTIBIOTIC PRESCRIPTION FILL RATES DECLINING IN THE U.S.

PUBLISHED **AUGUST 24, 2017**

EXHIBIT 4: TOTAL ANTIBIOTIC PRESCRIPTION FILL RATE BY STATE IN 2016 (PER 100 MEMBERS)



THIS STUDY FINDS...

9% DECLINE — **NOTABLE PROGRESS IN REDUCING** ANTIBIOTIC USE OVER THE **PAST SEVEN YEARS**

CHANGE IN ANTIBIOTIC FILL RATES

BROAD-SPECTRUM	DOWN 13%
ADULT	DOWN 6%
CHILDREN	DOWN 16%
INFANT	DOWN 22%

Antibiotic Prescription Rates Declining

Antibiotic prescription fill rates in the U.S. have been declining among the commercially insured population since 2010 (see Exhibit 1). There has been a 9 percent decline in fill rates from 2010 to 2016.

EXHIBIT 1: TOTAL ANTIBIOTIC PRESCRIPTION FILL RATES (PER 100 MEMBERS)

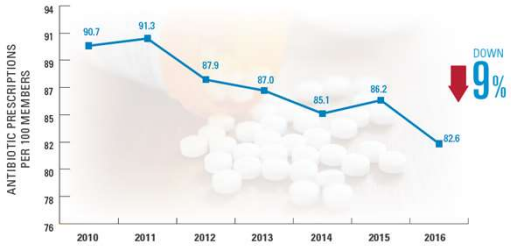


EXHIBIT 2: ANTIBIOTIC PRESCRIPTION FILL RATES BY TYPE OF ANTIBIOTIC (PER 100 MEMBERS)

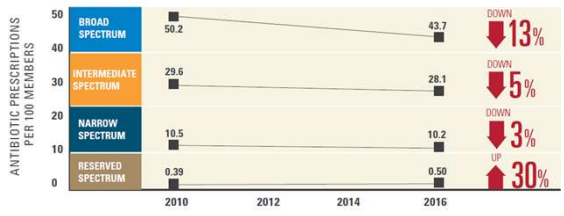
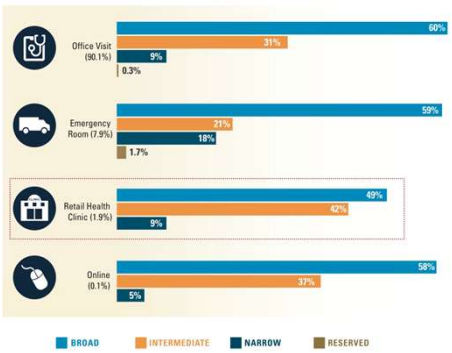
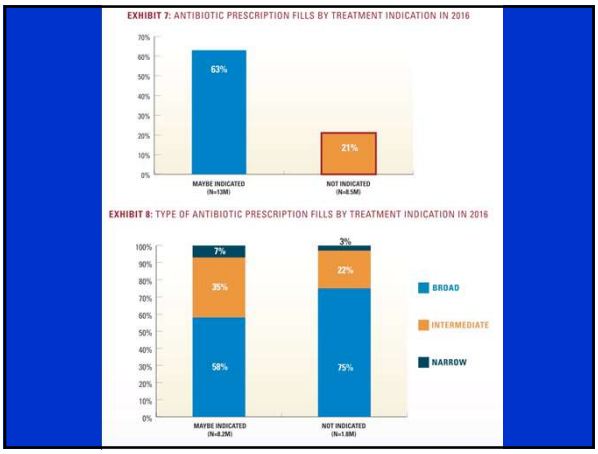
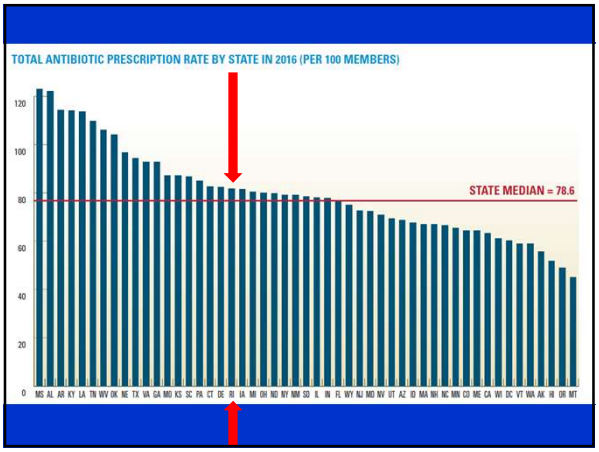


EXHIBIT 6: TYPE OF ANTIBIOTIC PRESCRIPTION FILLED BY SETTING OF CARE IN 2016







ANTIBIOTIC PRESCRIPTION RATES BY STATE AND METROPOLITAN STATISTICAL AREAS (MSAS)

STATE	RATE OF ANTIBIOTIC PRESCRIPTIONS FILLED PER 100 MEMBERS		PERCENT CHANGE IN ANTIBIOTIC PRESCRIPTIONS FILLED	RATE OF BROAD-SPECTRUM ANTIBIOTIC PRESCRIPTIONS FILLED PER 100 MEMBERS		PERCENT CHANGE IN BROAD-SPECTRUM ANTIBIOTIC PRESCRIPTIONS FILLED	RATE OF PEDIATRIC ANTIBIOTIC PRESCRIPTIONS FILLED PER 100 MEMBERS		PERCENT CHANGE IN PEDIATRIC ANTIBIOTIC PRESCRIPTIONS FILLED
	2010	2016	2010 to 2016	2010	2016	2010 to 2016	2010	2016	2010 to 2016
RI	96.2	81.8	-15%	53.2	42.4	-20%	93.6	75.3	-20%
National Average (Per 100 members)	90.7	82.6	-9%	50.2	43.7	-13%	96.7	80.8	-16%

How Can You be Good Stewards?

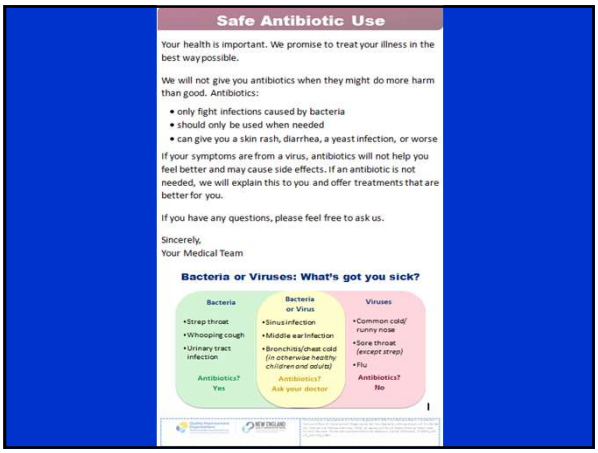
Avoid Antibiotics for Inappropriate Indications

- Upper respiratory tract infections (URTIs)
  - Colds, acute bronchitis, non-streptococcal pharyngitis
- Early or mild sinusitis
- Asymptomatic bacteriuria (ASB)
- Colonization of wounds

Educate Your Patients on When Antibiotics are and are Not Effective

- One of the most difficult obstacles practitioners face, especially in outpatient setting
- Discuss indications, appropriate use and risks of antibiotic use
- Recommend specific symptomatic relief and a back-up plan
- Constructively correct false popular beliefs

United States Centers For Disease Control And Prevention. Get Smart: Know When Antibiotics Work. URL: http://www.cdc.gov/getsmart/campaign-materials/posters.html [Accessed 2014 April 17]



Safe Antibiotic Use

Your health is important. We promise to treat your illness in the best way possible.

We will not give you antibiotics when they might do more harm than good. Antibiotics:

- only fight infections caused by bacteria
- should only be used when needed
- can give you a skin rash, diarrhea, a yeast infection, or worse

If your symptoms are from a virus, antibiotics will not help you feel better and may cause side effects. If an antibiotic is not needed, we will explain this to you and offer treatments that are better for you.

If you have any questions, please feel free to ask us.

Sincerely,
Your Medical Team

Bacteria or Viruses: What's got you sick?

Optimize Dose and Route of Antibiotic Administration

- IV-to-PO Switch
  - Antibiotics with adequate oral bioavailability
    - Doxycycline / minocycline, azithromycin, fluoroquinolones, fluconazole, linezolid, metronidazole, clindamycin

IV vs PO

- When using highly bioavailable agents, use PO if GI absorption intact
- Do not forget different class IV to PO switch
- Consider only PO therapy from the start

IV vs PO

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association

Association Between Initial Route of Fluoroquinolone Administration and Outcomes in Patients Hospitalized for Community-acquired Pneumonia

Raquel K. Bellott,[1,2] Tara Lagu,[1,2,3] Sarah Haessler,[1,2,4] Peter K. Lindenauer,[1,2,3] Penelope S. Pekow,[2,5] Aruna Priya,[2] Marya D. Zilberberg,[6] Daniel Skiest,[1,2,4] Thomas L. Higgins,[1,2,7] Mihaela S. Stefan,[1,2,3] and Michael B. Rothberg[2]

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DOI: 10.1093/cid/ciw209

Effective PO Options for MDR UTIs

- Treatment options for multi-drug resistant (MDR) Gram negative bacilli (GNB) are increasingly limited
- Most urinary tract infections (excluding urosepsis / complicated UTIs) in adults are due to acute uncomplicated cystitis (AUC) / catheter associated bacteriuria (CAB)
- The usual therapy for MDR GNB AUC is often IV and expensive

Interpretational Problems with UA & UC

Urine Specimens m*ust be transported rapidly to microbiology lab* and processed rapidly

UA:

- **Use *uncentrifuged urine* to *avoid clumping of WBCs***
- ***WBCs in clumps underestimates degree of pyuria***

Ucx:

- **Low initial bacterial counts → increase over time to high counts**
- **Bacterial colony counts ~ urinary pH and urinary osmolarity dependent**

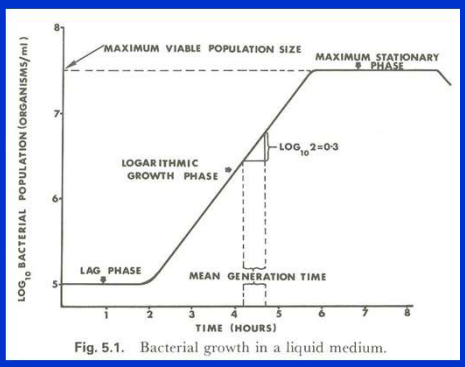


Fig. 5.1. Bacterial growth in a liquid medium.

Asscher AW, Sussman M, Waters WE, Davis RH, Chick S. Urine as a medium for bacterial growth. Lancet 1966 1: 1037-41

Factors in Antibiotic Selection

Key Factors

- **Appropriate Spectrum** (*based coverage of usual body site* flora)
- **Tissue Penetration** (*must achieve therapeutic concentration at site of infection*)
- "**Low Resistance Potential"** (*first do no harm*!)
- **Side Effect Profile** (*avoid antibiotics with high C. difficile potential*)

Factors in Antibiotic Selection

Unimportant Antibiotic Selection Factors

- **Bactericidal vs. bacteriostatic**
- **Synergy** (*rarely important and applicable to very few organisms*)

Primer on Antibiotic Resistance

High Level/Absolute Resistance

- **MIC beyond achievable serum concentrations**
- **Not site or concentration dependent**
  Example: gentamicin resistant *P. aeruginosa*

Primer on Antibiotic Resistance

Intermediate/Relative Resistance

- ***Susceptibility* is, in part, *concentration dependent***
- **Achievable concentrations > MIC *at site of infection* (urine/GU tract)**

Relative resistance is *site & concentration dependent*

Example: meropenem "resistant" *P. aeruginosa*

Antibiotic Resistance Potential

"High resistance potential" antibiotics:
antibiotics to avoid if possible

- **Ciprofloxacin**
  (S. pneumoniae, P. aeruginosa, ↑ MRSA)
- **TMP-SMX**
  (S. pneumoniae, E. coli)
- **Imipenem**
  (P. aeruginosa, ↑ MRSA)

Antibiotic Resistance Potential

"High resistance potential" antibiotics:
antibiotics to avoid if possible

- **Gentamicin/tobramycin**
  (P. aeruginosa)
- **Ceftazidime**
  (P. aeruginosa, ↑ MRSA)
- **Macrolide**
  (S. pneumoniae)

Antibiotic Resistance Potential

"Low resistance potential" antibiotics

IV

- Meropenem
- Ceftriaxone
- Piperacillin/tazobactam
- Aztreonam
- Cefepime
- Colistin/Polymyxin B
- Tigecycline

PO

- Doxycycline
- Minocycline
- Levofloxacin/Moxifloxacin
- Fosfomycin
- Methenamine salts
- Nitrofurantoin

Interpretation of Urine Susceptibility

Urinary Susceptibility *	Interpretation
S (susceptible)	Clinical effectiveness likely †
I (intermediate)	Effectiveness ~ urinary concentration
R (non-susceptible)	Maybe susceptible

***depends on urinary pH, antibiotic dose, and renal function**
† if in vitro = in vivo susceptibility

Cunha BA. Oral doxycycline for Non-systemic Urinary Tract Infections (UTIs) due to P. aeruginosa and other Gram Negative Uropathogens. Eur J Clin Microbiol Infect Dis 31:2865-2868, 2012.

Susceptibilities of "Ampicillin Resistant E. coli" Tested in Human Urine at Urinary pH and Urinary Concentrations

Oral Antibiotic	Broth pH 7.4		Urine[a] pH 6.0	
	% Susceptible	% Resistant	% Susceptible	% Resistant
Ampicillin	**0%** (0/25)	100% (25/25)	**64%** (16/25)	36% (9/25)
Amoxicillin	**28%** (7/25)	72% (18/25)	**100%** (25/25)	0% (0/25)
Doxycycline	**40%** (10/25)	60% (15/25)	**76%** (19/25)	24% (6/25)

[a] Human urine heat treated to remove thermolabile anti-bacterial activity

Ristuccia PA, Cunha BA. Activity of Antimicrobial Agents at Urinary Concentrations Against Ampicillin-Resistant E. coli in Human Urine. Advances in Therapy 3:163-167, 1986.

Cunha BA. Oral doxycycline for Non-systemic Urinary Tract Infections (UTIs) due to P. aeruginosa and other Gram Negative Uropathogens. Eur J Clin Microbiol Infect Dis 31:2865-2868, 2012.

Penicillin G: E. coli Urine vs Serum Spectrum

Dosage	Serum Concentration	Minimal Urine Concentration
800,000 units q6h	< 0.5 mcg/mL	100 mcg/mL
Penicillin – G Concentration		% E. coli killed
0.5 mcg/ml		0
100 mcg/ml		85

Stamey TA. Urinary Infections. Williams & Wilkins, Baltimore, 1972, pp 275-282.

Urinary Spectrum of Oral Penicillins [a]

Parameters	Penicillin	Ampicillin	Amoxicillin
Oral dose	500 mg	500 mg	500 mg
Serum levels	0.5 mcg/ml	2 mcg/ml	4 mcg/ml
Urine levels	> 100 mcg/ml	> 300 mcg/ml	> 600 mcg/ml
Urinary spectrum	E. coli, P. mirabilis, E. faecalis (VSE)[b]	E. coli, P. mirabilis, E. faecalis (VSE)[b]	E. coli, P. mirabilis, E. faecalis (VSE)[b]

[a] With normal renal function [b] MICs < 8 mcg/ml

Cunha BA. Oral doxycycline for Non-systemic Urinary Tract Infections (UTIs) due to P. aeruginosa and other Gram Negative Uropathogens. Eur J Clin Microbiol Infect Dis 31:2865-2868, 2012.

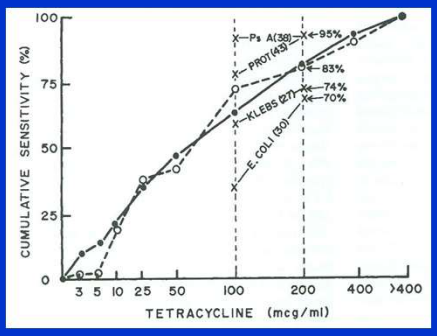
Urinary Spectrum of Oral Tetracyclines [a]

Parameters	Tetracycline	Doxycycline
Oral dose	500 mg	100 mg
Serum levels	2 mcg/ml	4 mcg/ml
Urine levels	> 300 mcg/ml	> 150 mcg/ml
Urinary spectrum	E. coli, Klebsiella sp., Enterobacter sp., Indole + Proteus sp., Pseudomonas aeruginosa[b]	E. coli, Klebsiella sp., Enterobacter sp., Indole + Proteus sp., Pseudomonas aeruginosa[b]

[a] With normal renal function [b] MICs < 150 mcg/ml

Cunha BA. Oral doxycycline for Non-systemic Urinary Tract Infections (UTIs) due to P. aeruginosa and other Gram Negative Uropathogens. Eur J Clin Microbiol Infect Dis 31:2865-2868, 2012.

Tetracycline: Urinary Spectrum



Musher DM, et al. Effectiveness of Achievable Urinary Concentrations of Tetracycline Against Tetracycline Resistant Pathogenic Bacteria. JID 131: 540-44, 1975.

Parameters	Methenamine salts (methenamine hippurate/mandelate)	Fosfomycin
Oral dose	100 mg	3 gm
Serum levels	Formaldehyde level = 0	26 mcg/ml
Urine levels	Formaldehyde > 20 mcg/ml (dependent on urine pH, time, volume)	1000-4000 mcg/ml
Urinary spectrum	E. coli, Klebsiella sp., Enterobacter sp., Serratia marcescens, P. aeruginosa	E. coli, Klebsiella sp., Enterobacter sp., Serratia marcescens, P. aeruginosa

Cunha BA. Oral doxycycline for Non-systemic Urinary Tract Infections (UTIs) due to P. aeruginosa and other Gram Negative Uropathogens. Eur J Clin Microbiol Infect Dis 31:2865-2868, 2012.

Nitrofurantoin

- Spectrum includes all GNB uropathogens *except*:
  - *Pseudomonas aeruginosa*
  - *Serratia marcescens*
  - *Proteus mirabilis*
- Also effective against all Gram positive uropathogens (VSE & VRE) *except*:
  - Group B streptococci
- Resistance is rare after decades of worldwide use

Nitrofurantoin

- For MDR GNB AUC, there are few oral alternatives, particularly for carbapenem resistant Enterobacteriaciae (CRE)
  - Doxycycline
  - Fosfomycin
  - Fluoroquinolones
- Antimicrobial activity is pH dependent
- Renal tubular re-absorption is pH dependent

The Effects of Urinary pH on Antibiotic Activity

Parameter	Antibiotic
Optimal activity at urinary pH (pH 5.5-6)	Penicillin G Trimethoprim-sulfamethoxazole (TMP-SMX) Oral cephalosporins
Activity not affected by urinary pH	Ampicillin Nalidixic acid / oxolinic acid Chloramphenicol
Activity increased by acid urine (pH < 6)	Tetracycline
Activity requires an acid urine (pH < 6)	Methenamine mandelate / methenamine hippurate
Activity increased by alkaline urine (pH > 6)	Erythromycin Aminoglycosides

Nitrofurantoin

- After appropriate spectrum, main concern of nitrofurantoin efficacy is renal insufficiency, i.e., reduced CrCl (< 60 ml/min)
- Currently, nitrofurantoin is not recommended for CrCl < 60 ml/min
- There is little clinical data to support this break-point
- Clinically, nitrofurantoin is highly effective in patients with CrCl > 30 ml/min

Nitrofurantoin

- Nitrofurantoin is effective oral therapy for AUC (due to susceptible organisms) in patients who have renal insufficiency (CrCl = 30-60 ml/min), particularly in those with an optimal urinary pH (acidic)
- Nitrofurantoin has several advantages:
  - Oral vs IV option
  - Low resistance potential
  - Useful in renal insufficiency

Nitrofurantoin

- Patient presenting with AUC / CAUTI caused by MDR uropathogens may be treated with oral antibiotics
  - Doxycycline
  - Nitrofurantoin
  - Fosfomycin
  - Methanamine salts
- Oral options provide cephalosporin, aminoglycoside, quinolone, and carbapenem sparing therapies
- Oral options often less expensive, have lower resistance potential, lower C. diff potential and may prevent hospitalization

Conclusion

- Successful ASPs require adequate resources, collaboration, and expertise
- Excessive / poorly chosen antibiotic therapy will impact both individual patients and the community at large
- Using existing antibiotics wisely can minimize development of MDROs

Be Good Antimicrobial Stewards

How we use antibiotics today or in one patient directly impacts how effective they will be tomorrow or in another patient; they are a shared resource

- Centers for Disease Control and Prevention