Antimicrobial Stewardship: Maximizing Antimicrobial Utilization

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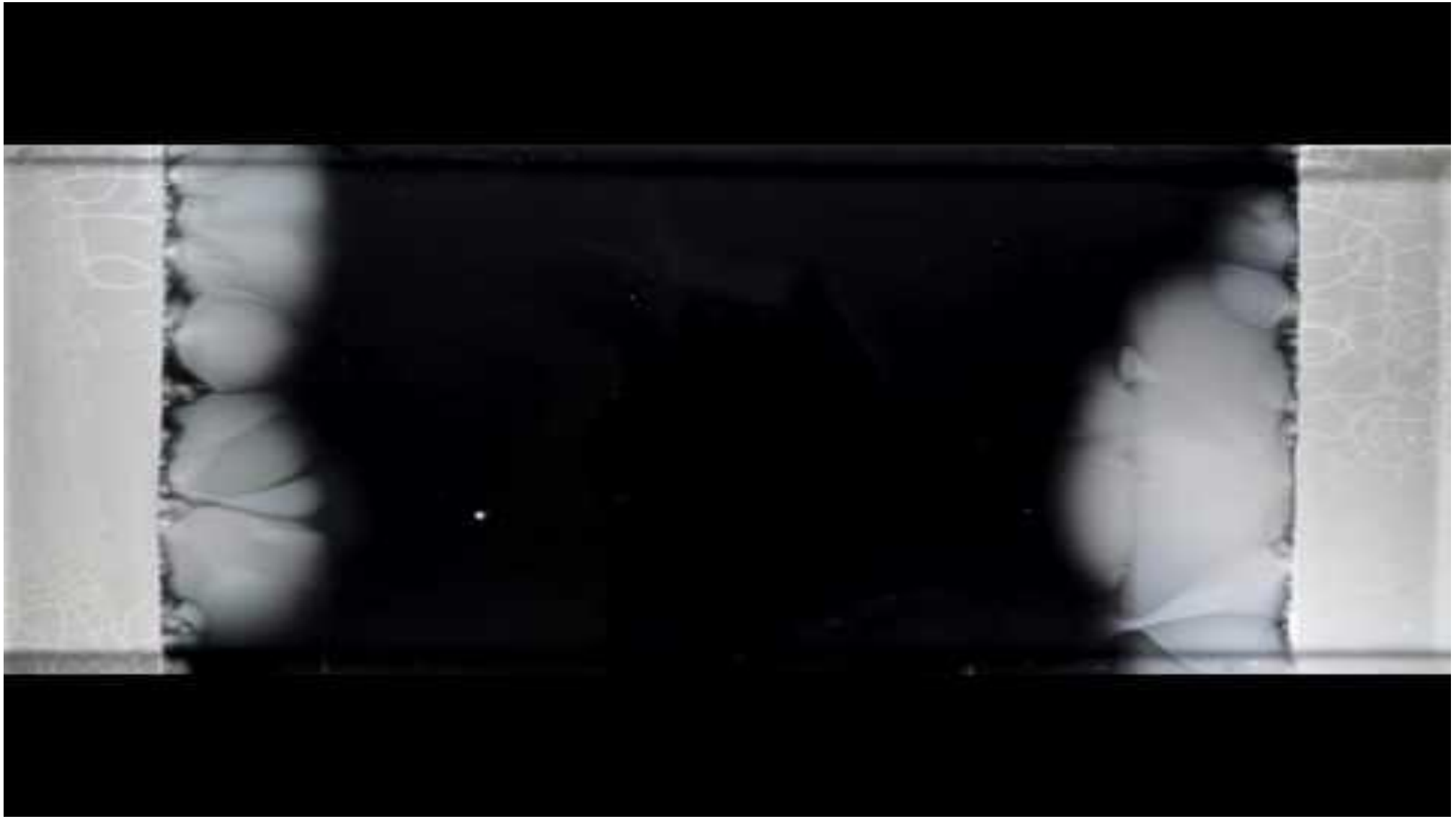
Disclosure

I do not have relevant financial relationships with commercial interests.

Objectives

- Describe the key targets of an antimicrobial stewardship program.
- Analyze the potential gaps new technology can fill in your current clinical practice.
- Describe the factors to consider for antibiotic selection for common infectious diseases

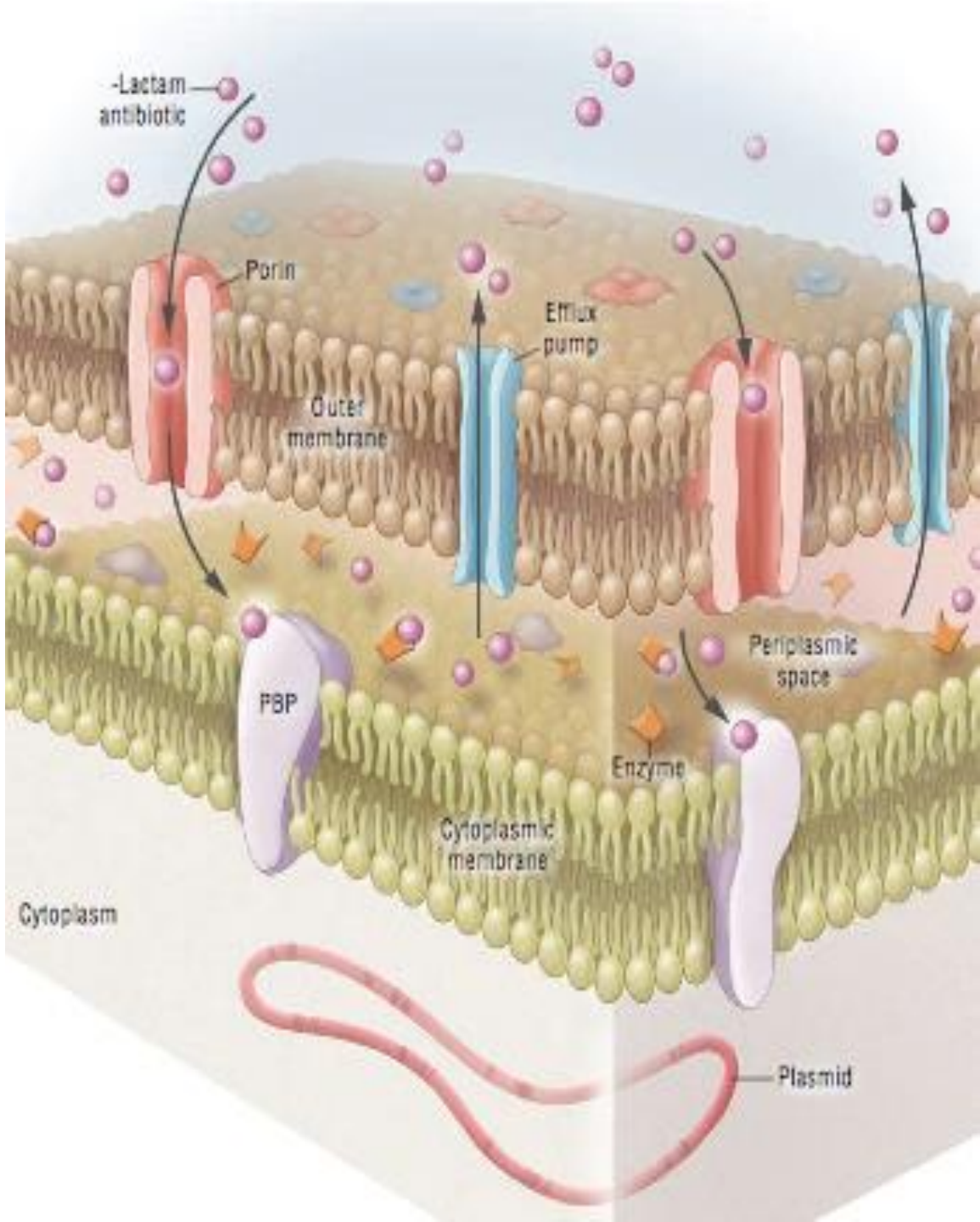
Bacteria can develop drug resistance rapidly



https://www.youtube.com/watch?v=plVk4NVIUh8&feature=youtu.be

The Challenge: Multiple Mechanisms of Resistance

1. Production of hydrolytic or modifying enzymes
2. Alteration of targets such that they are no longer susceptible to antibacterial action
3. Modification of target accessibility
   - Permeability barrier
   - Energy-dependent antibiotic efflux pumps



Xian-Zhi et al. Drugs 2004

Drug class specific mechanisms of resistance

Drug	Bacterial target	Mechanism of resistance
β-lactams	Cell wall synthesis (PBPs)	β-lactamases, alteration of PBPs, permeability barrier, active efflux
Aminoglycosides	Protein synthesis	Aminoglycoside-modifying enzymes, alterations of ribosomes, permeability barrier, active efflux
Quinolones	DNA synthesis (DNA gyrase, topoisomerase IV)	Alteration of DNA gyrase and topoisomerase IV, active efflux
Polymyxins	Cell membranes	Alterations of LPS

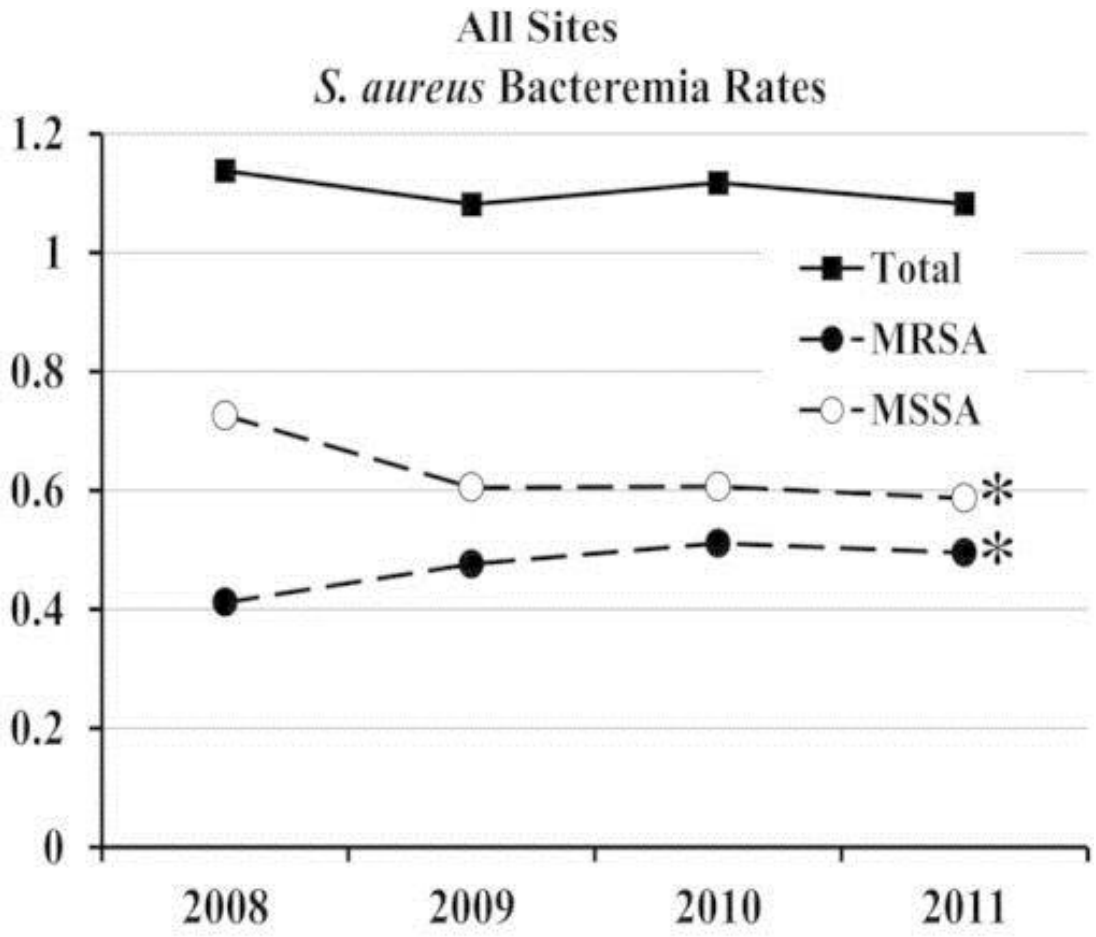
Xian-Zhi et al. Drugs 2004

Which organisms are affected by overuse?

Urgent Threat	*C. difficile* Carbapenem-resistant Enterobacteriaceae (CRE) Drug-resistant *Neisseria gonorrhoeae*
Serious Threat	Multidrug-resistant (MDR) *Acinetobacter* Drug-resistant *Campylobacter* Fluconazole-resistant *Candida* Extended Spectrum β-lactamase producing Enterobacteriaceae (ESBL) Vancomycin-resistant *Enterococcus* (VRE) MDR *Pseudomonas aeruginosa* Drug-resistant Non-typhoidal *Salmonella* Drug-resistant *Shigella* Methicillin-resistant *Staphylococcus aureus* (MRSA) Drug-resistant *Strep pneumoniae* Drug-resistant tuberculosis

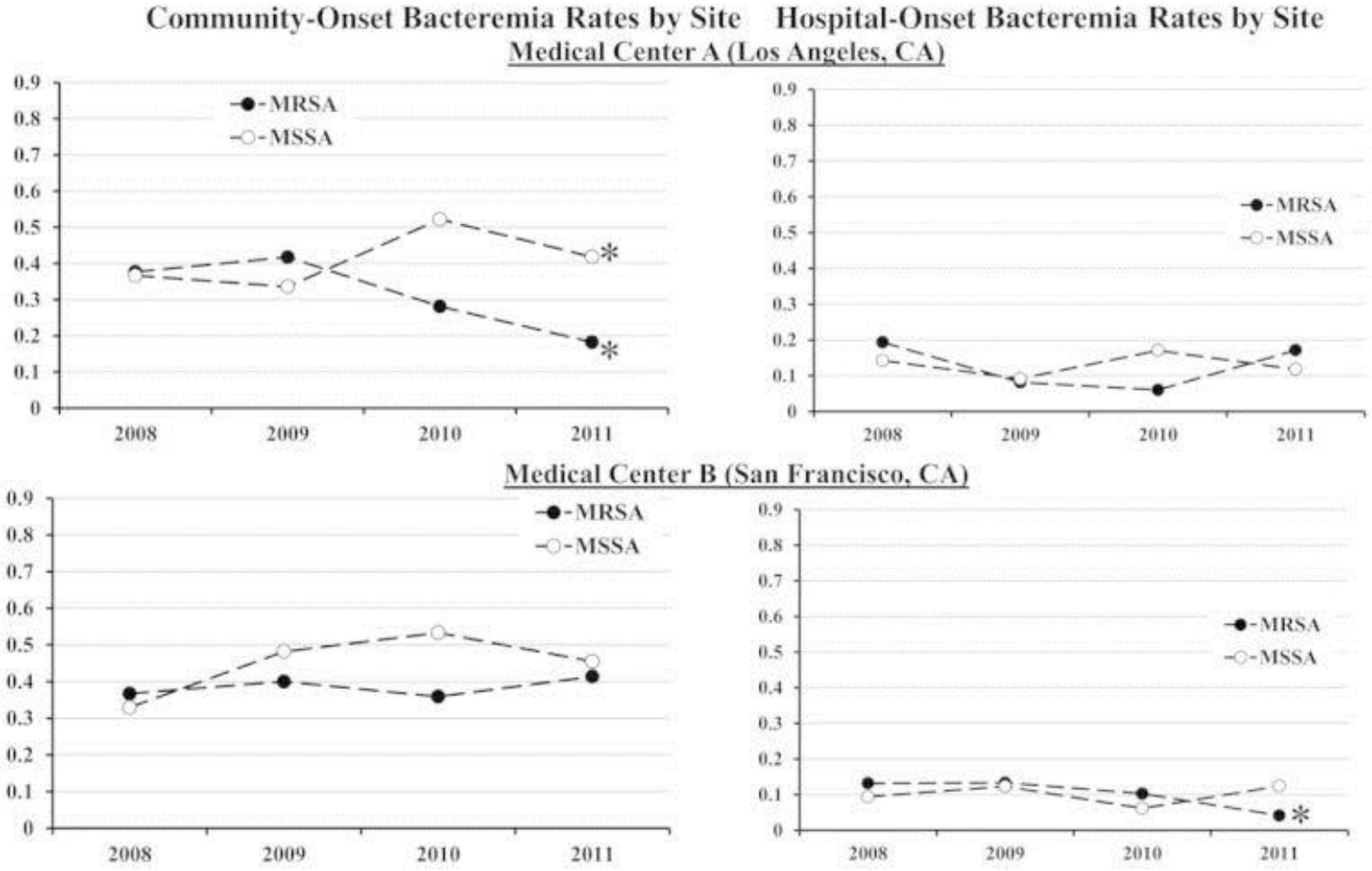
http://www.cdc.gov/drugresistance/threat-report-2013

Epidemiology of *Staph aureus* Bacteremia



David MZ et al. Clin Infect Dis. 2014 Sep 15; 59(6): 798–807.

West Coast Rates

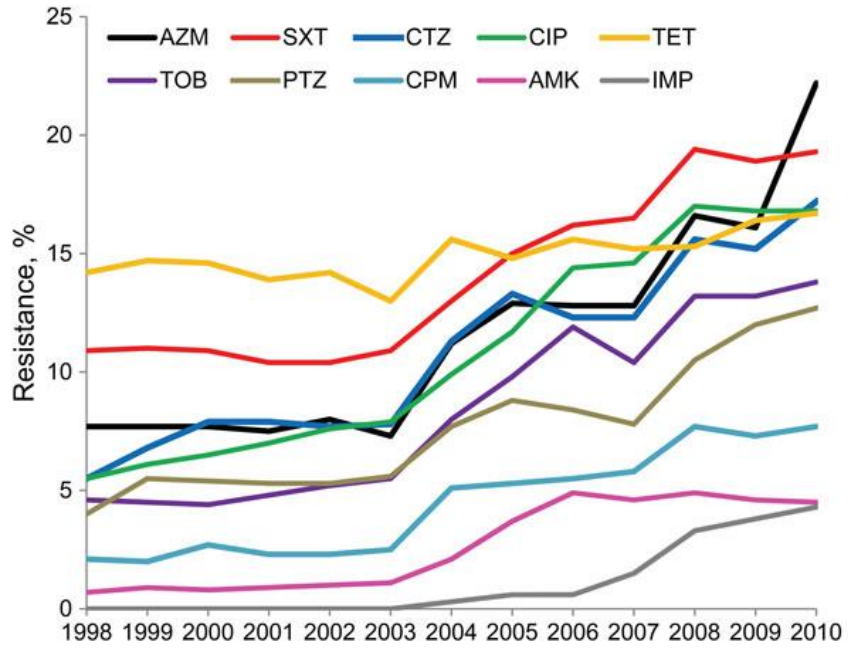


David MZ et al. Clin Infect Dis. 2014 Sep 15; 59(6): 798–807.

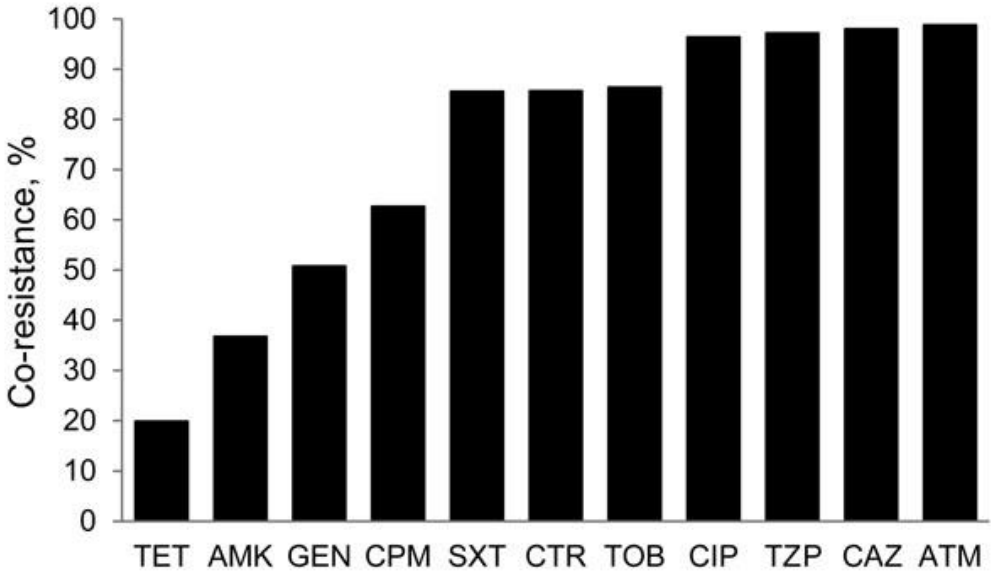
The Problem with Gram negatives

- More inherently resistant than Gram-positive
  - Due to cooperation between OM barrier and expression of broad-specificity multidrug efflux pumps
  - Also possess drug-specific efflux pumps which mediate resistance to certain classes of antimicrobials

US Resistance Rates of *K. pneumoniae*



Cross resistance among imipenem resistant *K. pneumoniae*



Sanchez GV, et al. *Emerging Infectious Diseases*. 2013;19(1):133-136.

CDC: Antibiotic Resistance Threats in the US

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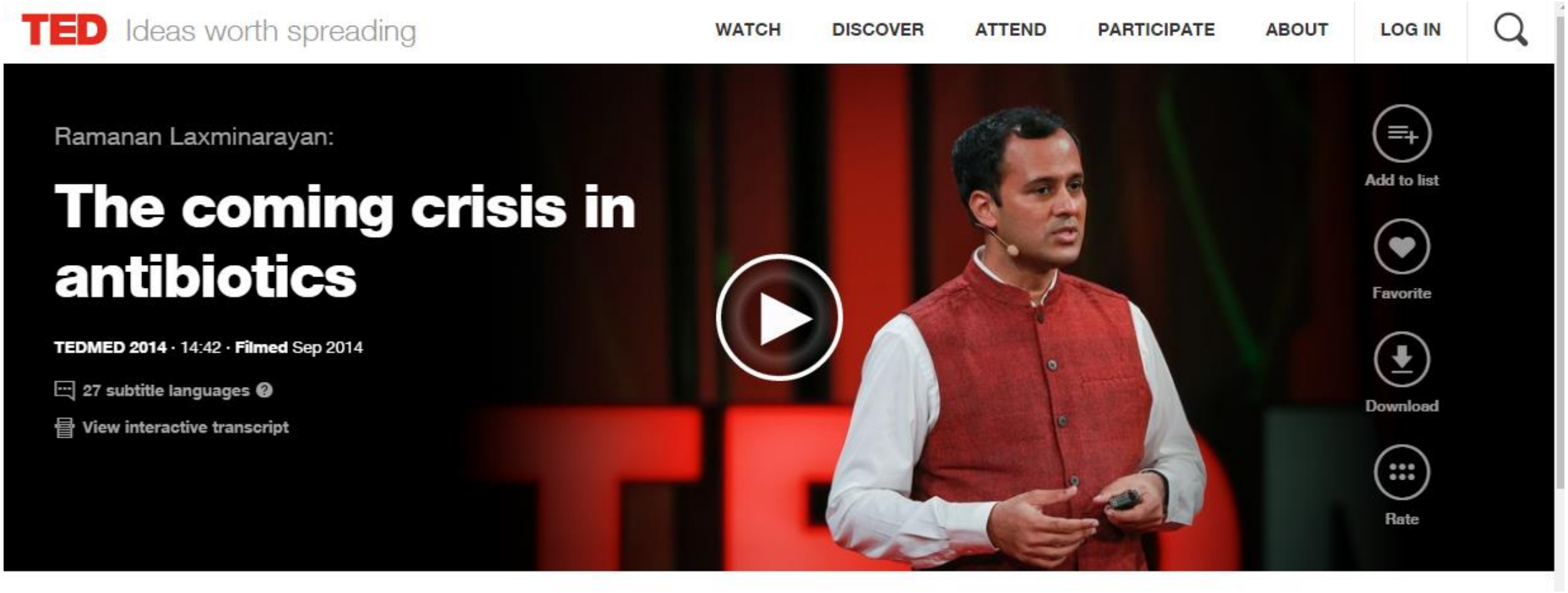
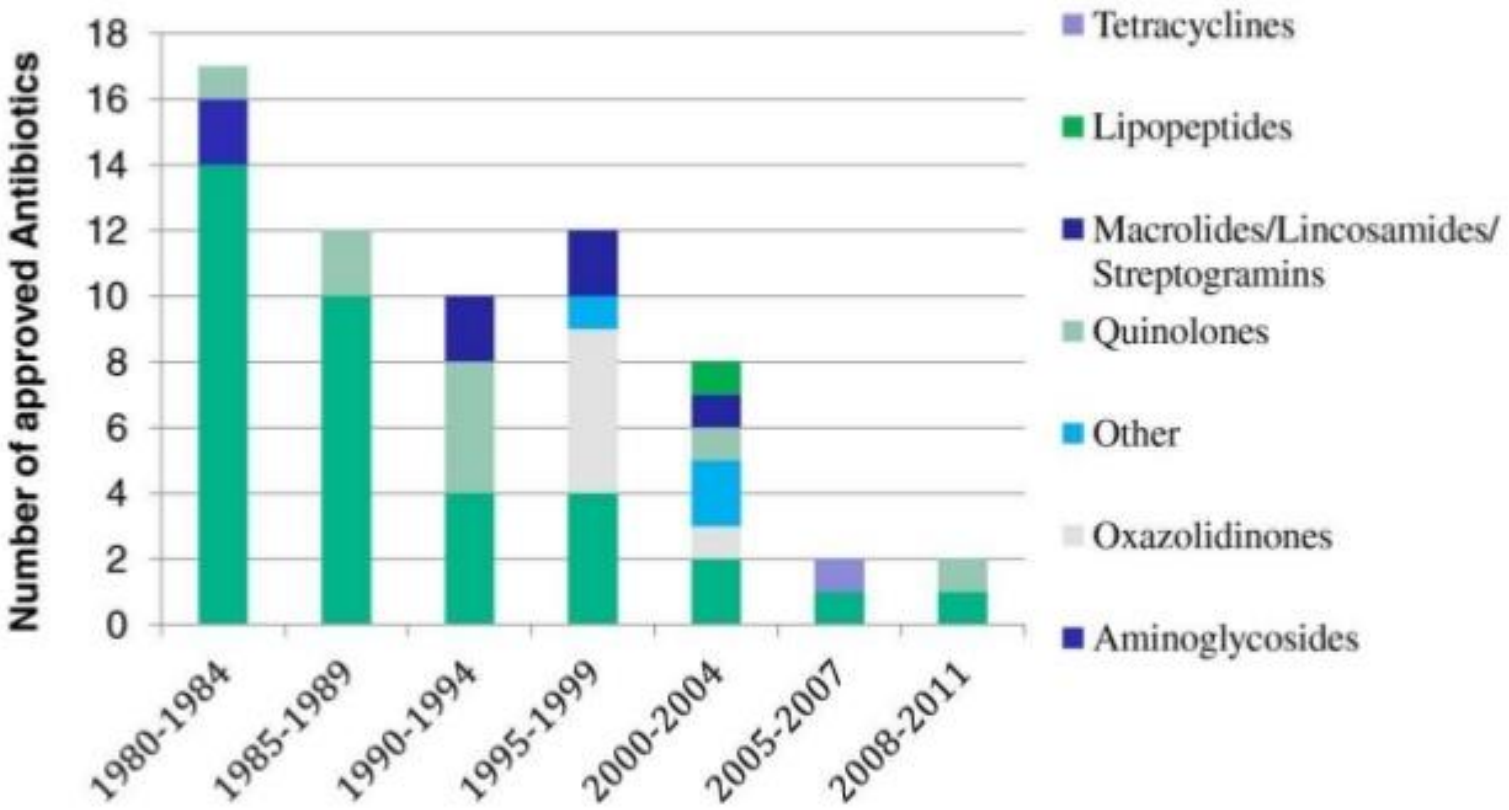
What can we do?

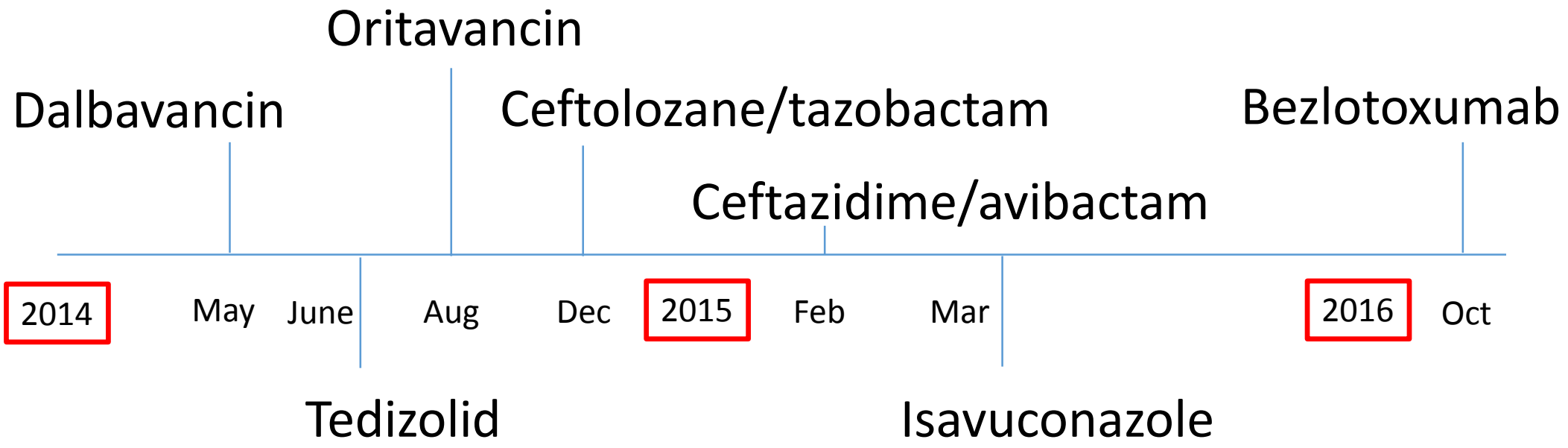


https://www.ted.com/talks/ramanan_laxminarayan_the_coming_crisis_in_antibiotics

Declining Antibiotic Pipeline



New FDA Approved Drugs



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Practical Application of Newly approved antibiotics

	FDA Approved Indications	Available dosage forms	What's special about it?	Cost*
Dalbavancin Oritavancin	SSTI, including MRSA	IV	Long acting (only one IV dose needed)	$5,364/cour $3,480/cour
Tedizolid	SSTI, including MRSA	IV/PO	Once daily dosing, less toxicity compared to linezolid?	PO: $386/day
Ceftolozane/tazobactam Ceftazidime/avibactam	Complicated UTI/ intra-abdominal infection	IV	Activity against MDR gram negative organisms (CRE- Ceftaz/avi)	$300 $855
Isavuconazole	Invasive Aspergillosis, mucormycosis	IV/PO	Less drug interactions, toxicity	PO: $192/day IV: $327/day
Bezlotoxumab	Adjunct therapy for *C. difficile* infection	IV	Monoclonal antibody against toxin B	$4560

Vancomycin (IV): $150/course

Meropenem: $50
Colistin: $70

*AWP Pricing

Primary Goal of ASP

Goal: optimize the utilization of antimicrobial agents in order to improve clinical outcome while minimizing unintended consequences:

- Selection of pathogenic organisms (*C. difficile*)
- Toxicities
- Emergence of resistant pathogens

Barlam TF, et al. Clin Infect Dis. 2016 May 15;62(10):1197-202.

Unintended Consequences: Collateral Damage

"Collateral Damage": ecological adverse effects of antibiotic therapy; selection of drug-resistant organisms and the unwanted development of colonization or infection with MDR organisms

Patient Level

- Antibiotics cause severe disruption of gut microbiota
  - Decrease in taxonomic richness and diversity → metabolic activity and products
  - Within 4 weeks after withdrawal of abx, microbiota may return to overall composition similar to what it was pre-exposure
  - Decrease in "colonization resistance" → increase risk for colonization with *C difficile* spores

Institution Level

- Increasing rates of ESBL, CRE, MDR gram negative organisms on Antibiogram

Lopez CA, et al. Cell Host Microbe. 2014 Aug 13;16(2):156-63. doi: 10.1016/j.chom.2014.07.009.

GUT Trivia

How many species of bacteria live in your gut?

A. 100
B. 1,000
C. 10,000
D. 100,000
E. 1 million

What concentration of organisms can be found in the small intestine?

A. It depends
B. 10^2
C. 10^4
D. 10^6
E. 10^8
F. 10^{10}

In the colon?

A. 10^2
B. 10^5
C. 10^7
D. $>10^{11}$

Healthy Adults have Colonization Resistance

- Mechanism where intestinal microflora protects itself against incursion by new, potentially harmful bugs
  - Protects healthy adults from *C difficile* colonization and disease
  - Protection lost by disease states (inflammatory bowel disease) or other disruption (antibiotics, chemotherapy)

Limiting Overexposure to Antibiotics

ASP Targets

For every patient

- Right drug, right time, right duration, right disease state
- De-escalation

Institution/Health System level

- Utilizing resistance concepts
- Minimizing collateral damage
- Maximizing PK of antibiotics
- Improving procedures to prevent adverse events

Targets must be tailored to the institution's needs

Can resistance be reversed?

Interventional Campaign to Limit FQ Prescribing at a 525-bed community teaching hospital in Los Angeles County

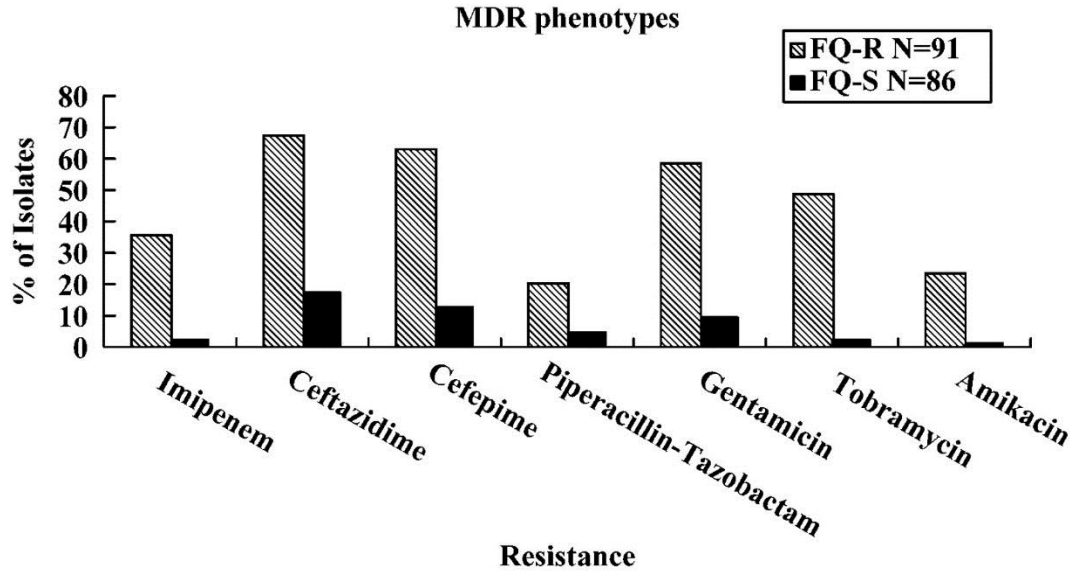
- Why is *Pseudomonas aeruginosa (Psa)* such a problem?
  - Rates of mortality up to 60%
  - Economic burden: more ICU admission, longer LOS

- Managing Psa infections is clinically challenging due to its ability to easily acquire resistance
  - Fluoroquinolone (FQ) resistant *Psa* are often multi-drug resistant
  - MDR *Psa* infections associated with higher mortality rates

Nguyen LH, et al. J Antimicrob Chemother. 2008 Mar;61(3):714-20.
Werth BJ, et al. Am J Infect Control. 2015 May 1;43(5):465-8.
Gasink LB, et al. Am J Med 2006;119:526.e19-25.

The Problem Identified…

- FQ susceptibility to Psa was 43%
  - Many were cross resistant with other abx classes
- FQ-R Psa infections → ↑ LOS by 5 days, 3x ↑for mortality

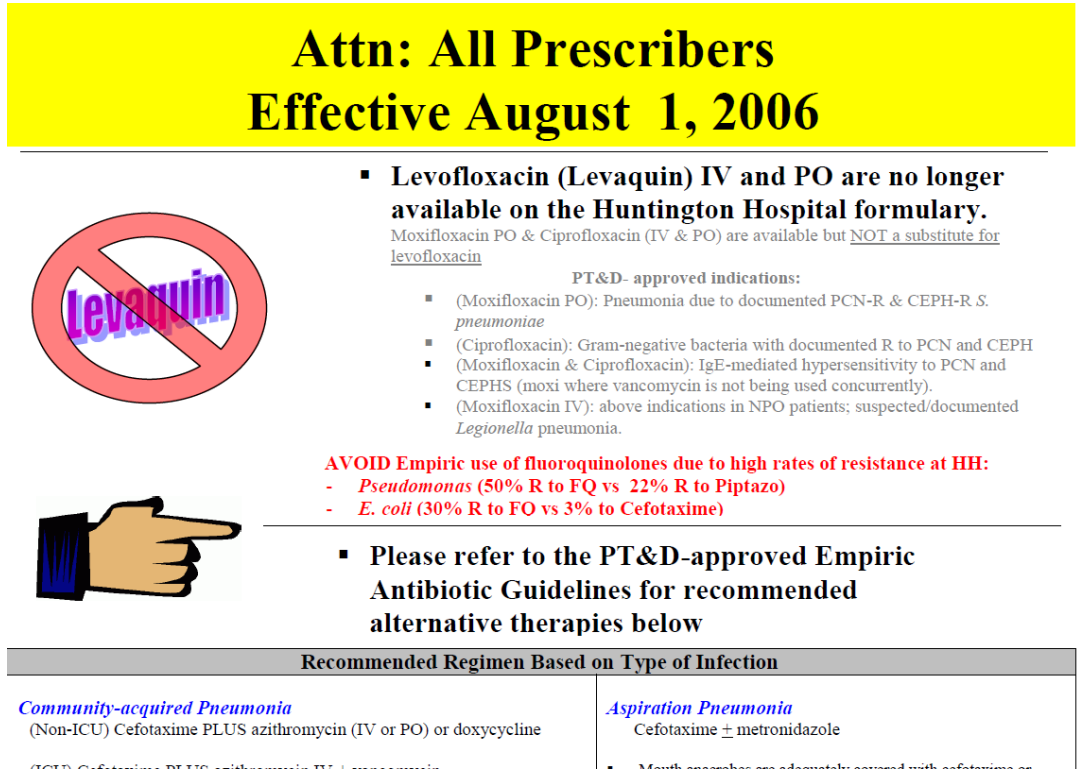


Nguyen LH, et al. J Antimicrob Chemother. 2008 Mar;61(3):714-20.
Hsu DI, et al. J Antimicrob Chemother. 2005 Apr;55(4):535-41.

1 year Campaign to Limit Levofloxacin Use

- "Consider beta lactams as first line therapy…"
- "misconception of FQ being more potent than beta lactams…"
- "negative consequences of FQ overuse…"

- Education and real-time feedback to prescribers provided over 1 year period
  - One year later, levofloxacin was removed from the formulary



Attn: All Prescribers
Effective August 1, 2006

- **Levofloxacin (Levaquin) IV and PO are no longer available on the Huntington Hospital formulary.**
  Moxifloxacin PO & Ciprofloxacin (IV & PO) are available but NOT a substitute for levofloxacin

PT&D- approved indications:

- (Moxifloxacin PO): Pneumonia due to documented PCN-R & CEPH-R *S. pneumoniae*
- (Ciprofloxacin): Gram-negative bacteria with documented R to PCN and CEPH
- (Moxifloxacin & Ciprofloxacin): IgE-mediated hypersensitivity to PCN and CEPHS (moxi where vancomycin is not being used concurrently).
- (Moxifloxacin IV): above indications in NPO patients; suspected/documented *Legionella* pneumonia.

AVOID Empiric use of fluoroquinolones due to high rates of resistance at HH:
- ***Pseudomonas* (50% R to FQ vs 22% R to Piptazo)**
- ***E. coli* (30% R to FQ vs 3% to Cefotaxime)**

- **Please refer to the PT&D-approved Empiric Antibiotic Guidelines for recommended alternative therapies below**

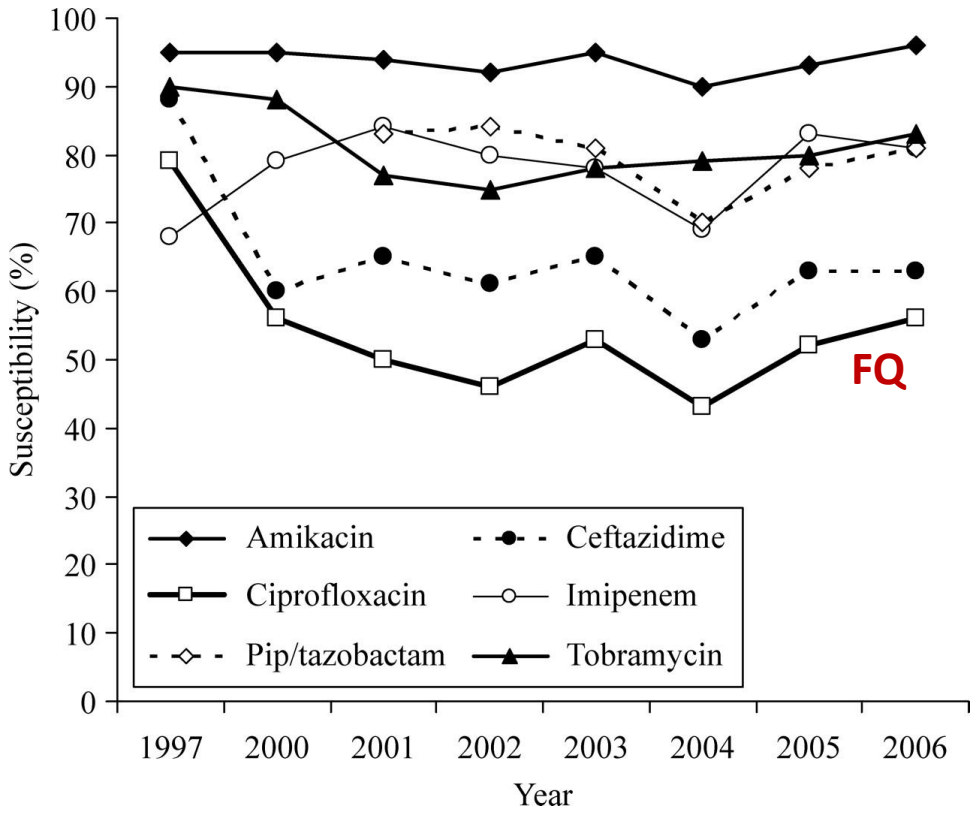
Recommended Regimen Based on Type of Infection	
Community-acquired Pneumonia (Non-ICU) Cefotaxime PLUS azithromycin (IV or PO) or doxycycline	***Aspiration Pneumonia*** Cefotaxime ± metronidazole

Nguyen LH, et al. J Antimicrob Chemother. 2008 Mar;61(3):714-20.

Improved Outcomes

Post-intervention data: 30% decrease in empiric FQ use→

- Improved clinical outcomes
  - Decreased in length of stay by 10d!
  - Decreased in mortality by 50%
- Improved resistance pattern
  - Increased FQ susceptibility (2016- 76% susceptible)



Lee H. Nguyen et al. J. Antimicrob. Chemother. 2008;61:714-720

Methods to Cut Unnecessary Exposure

Target: Cutting Unnecessary Exposure

- Up to 50% of antibiotic use in hospitals are unnecessary or inappropriate
- In order to improve appropriate antibiotic prescription
  - Accurate diagnosis
  - Timely identification and resistance pattern of infecting organism
  - Patient characteristics: comorbidities, age, etc.
- Delay of administration of effective antibiotic therapy have been shown to significantly impact morbidity and mortality (OR 1.88, 95% CI 1.29-2.72)
- We need a sensitive and specific tool to increase effectiveness of ASP

Hecker MT et al. Arch Intern Med 2003;163:972-978.
Iregui M, et al. Chest. 2002;122(1):262-268.
Fraser A, et al. Am J Med 2006; 119:970-6.

New Technology- “Rapid Diagnostics”

- Improved patient outcomes
  - Decrease hospital length of stay
  - Decrease ICU stay
  - Decreased mortality
  - Decrease unnecessary antibiotic exposure
- Improve identification of previous methods that had low sensitivity/specificity
  - *C difficile*
  - TB

Most common infectious diseases seen in outpatient and inpatient visits

- Most frequent principal illness-related reason for visit: cough
- 7th leading primary diagnosis groups for office visits in the US in 2013: acute upper respiratory infection, excluding pharyngitis
- Infectious and parasitic disease is the most frequent primary diagnosis of ED visits in 2013
  - Acute upper respiratory tract infections
  - Cellulitis and abscess
  - UTI
  - Otitis media

CDC website. https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2013_namcs_web_tables.pdf
https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2014_SHS_Table_P-10.pdf

Available Rapid Flu Diagnostics

Method	Types detected	Acceptable Specimens	Test Time	Sensitivity/specificity
Rapid Flu Diagnostic tests (antigen)	A and B	NP, nasal, throat swab	<15 min	50-70% / 90-95%
Rapid Molecular Assay (nucleic acid detection)	A and B	NP, nasal swab	<20 min	97- 100% / 95-98%
Immunofluorescence staining	A and B	NP, bronchial wash, nasal or ET aspirate	1-4 hours	
RT-PCR	A and B	NP, throat , swab, NP or bronchial wash, nasal or ET aspirate, sputum	1-8 hours, varies by assay	
Rapid cell culture	A and B	NP, throat swab, NP or bronchial wash, nasal or ET aspirate, sputum	1-3 days	

Popowitch EB, et al. J Clin Microbiol. 2015 Aug;53(8):2720-1.
CDC website. https://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm

Group A Strep Pharyngitis

- Rapid Antigen Detection Test (RADT)- high specificity 95%, but sensitivity 70-90%
- Throat culture – gold standard 90-95% sensitive
- Neither test accurately differentiate acutely infected persons from asymptomatic streptococcal carriers with intercurrent viral pharyngitis
- In children and adolescents, negative RADT test→ should perform throat culture for confirmation
- In adults, negative RADT test → not necessary to do throat culture
- Testing not recommended
  - If clinical symptoms strongly suggest viral etiology (cough, rhinorrhea, hoarseness, oral ulcers)
  - If <3 yo, as acute rheumatic fever is rare in this age group
- Testing or empiric treatment of asymptomatic household contacts not recommended

Shulman ST, et al. CID ; 2012 ; 55 : 86 -102

Is it MRSA or not?

Alere PBP2a Test

Sensitivity 98.1%; Specificity 98.8%
Results in 6 min after identification of *S. aureus*

Verigene Gram-Positive Blood Culture Test

Sensitivity 92.6-100%; Specificity 95.4-100%
Results in 2.5 hr after culture positivity

Prior to Availability of Susceptibilities

Sample Culture Report - Verigene

BLOOD CULTURE

SPECIMEN	Blood
SPECIAL REQUESTS	Left Hand
GRAM STAIN	Anaerobic bottle: Gram positive cocci in clusters Called result(s) to, and read back by Arlene 126071 4TH @ 0636 06/22/2015 Aerobic bottle: Gram positive cocci in clusters
	Staphylococcus aureus DETECTED by Verigene nucleic acid test. (mecA)NOT detected by Verigene nucleic acid test. Verigene rapid molecular assay tests for the following organisms: Staphylococcus species, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus lugdunensis, Enterococcus faecalis, Enterococcus faecium, Streptococcus species, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus anginosus group and Listeria species. Emailed report to Pharmacy 1345 6/22/15
CULTURE	Staphylococcus aureus 2 of 2 sets positive. Unless otherwise specified, performed at:

Vancomycin → Oxacillin or Cefazolin

Prior to Availability of Susceptibilities

Sample Culture Report – Alere PBP2a test

Staphylococcus aureus Isolated from Aerobic Blood Bottle
Oxacillin susceptible by PBP2a test.
This isolate has been shown to be a beta-lactamase producing strain.
Please note that beta-lactamase positive Staphylococci are resistant to penicillin, amino-, carboxy-, and ureidopenicillins.
.
Critical Value called to:
Location: 4A
Date & Time: 02/22/17 22:35 LT
Result: Gram positive cocci in clusters
Read Back? (Y/N): Y
.
Anaerobic Blood Bottle - No Growth at 5 Days

Vancomycin → Oxacillin or Cefazolin

Now you have the diagnosis and decide to treat…

Which antibiotic to choose?

Antibiotic Selection

Factors to consider

- Pharmacokinetics/Pharmacodynamics
- Empiric therapy vs directed therapy
  - Know the local antibiogram
  - Does MIC matter?
- Known clinical efficacy of drug to treat bug
- Toxicity Risk
- Collateral Damage
- Drug Allergies

Know the local antibiogram

LAC-USC Medical Center Jan 2016-Dec 2016 Reported as % susceptible	# of isolates	Ampicillin	Clindamycin	Ceftriaxone	Cefotaxime	Daptomycin	Erythromycin	Gentamicin syner.	Levofloxacin	Linezolid	Oxacillin	Penicillin	TMP/SMX	Tetracycline	Vancomycin
MRSA	656	-	71	-	-	79[a]	12	-	-	100	-	-	89	93	100
MSSA	1264	-	83	-	-	-	74	-	90	100	100	22	98	95	100
Vancomycin susceptible E faecium	58	72	-	-	-	-	21	93	83	100	-	67	-	-	100
Vancomycin susceptible E faecalis	343	99	-	-	-	-	8	72	82	100	-	99	-	27	100
VRE faecium	56	2	-	-	-	-	-	80	-	100	-	-	-	39	-
Streptococcus pneumoniae	63	-	-	94 * 100 **	99* 100 **	-	82	-	100	-	-	69* 100 **	73	79	100
Rate of MRSA 34%; VRE faecalis 1.2%; VRE faecium 49%															

LAC-USC Medical Center Jan 2016-Dec 2016 Gram Negatives Reported as % susceptible	# of isolates	Ampicillin	Amp/sulbact	Cefoxitin	Cefepime	Ceftriaxone	Meropenem	Gentamicin	Ciprofloxacin	TMP/SMX	Pip/tazo	Nitrofuran.	Fosfomycin
Acinetobacter baumanii	49	-	96	-	90	12	92	96	88	94	82	-	-
Enterobacter cloacae	189	-	-	-	96	78	100	97	95	91	83	-	-
Non-ESBL E coli	630	41	50	91	99	97	100	89	76	61	96	-	-
ESBL E coli	214	-	-	67	-	-	99	51	16	27	85	-	-
Non-ESBL Kleb pneumoniae	438	-	82	90	100	98	100	98	96	91	93	-	-
ESBL Kleb pneumoniae	42	-	-	93	-	-	100	45	52	29	76	-	-
Proteus mirabilis	178	79	91	92	99	98	99	85	85	81	99	-	-
Pseudomonas aeruginosa	538	-	-	-	85	-	88	89	81	-	87	-	-
Serratia marscecens	123	-	-	-	99	94	100	99	96	100	50	-	-
Rate of ESBL E coli 25%; ESBL Kleb pneumoniae 9%; CRE E coli 2 isolates; CRE Kleb pneumoniae 7 isolates													
URINE ISOLATES ONLY													
Non-ESBL E coli	2975	44	54	93	100	99	100	90	75	62	96	97	-
ESBL E coli	644	-	-	70	-	-	99	48	16	35	88	86	94
Non-ESBL Kleb pneumoniae	494	-	83	93	99	99	100	97	93	89	95	53	-
ESBL Kleb pneumoniae	81	-	-	88	-	-	98	40	41	20	78	30	-
Pseudomonas aeruginosa	229	-	-	-	94	-	95	90	81	-	90	-	-
Rate of ESBL E coli 18%; ESBL Kleb pneumoniae 14%; CRE E coli 5 isolates; CRE Kleb pneumoniae 8 isolates													

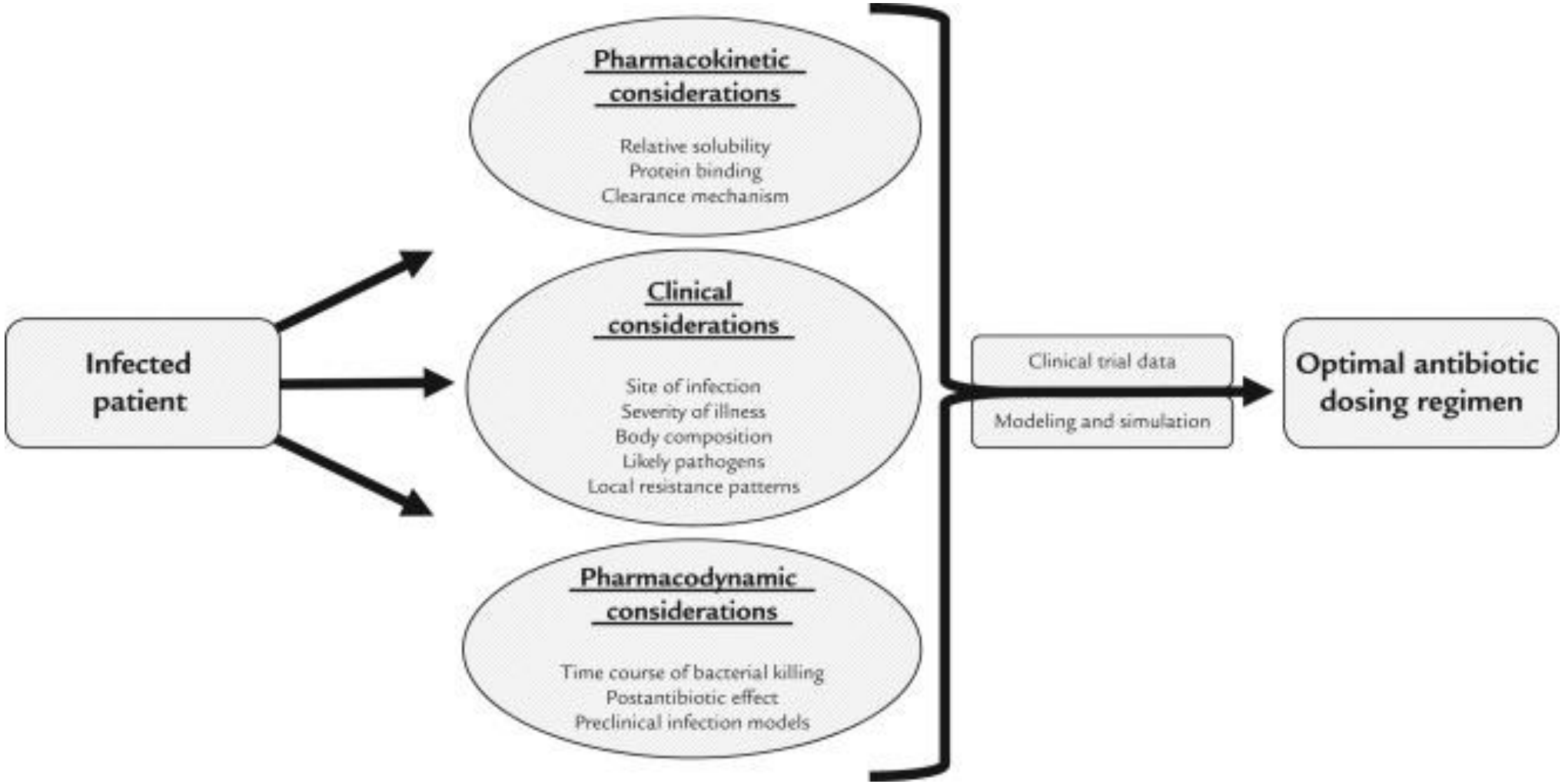
How does PK/PD factor into antibiotic selection?

- Antibiotic therapy sometimes fails to cure infections caused by apparently susceptible strains of bacteria

Host-related factors	Infection site-related factors	Bacteria-related factors
• Altered pharmacokinetics • Inadequate delivery of antibiotic to infection site • Protein binding • Immune deficiency	• Low pH • Low oxygen tension • High conc of cations	• High inoculum • Stationary-phase growth • Undetected resistance mechanisms • High spontaneous mutation frequency

Aeschlimann. Pharmacotherapy 2003.

Dose optimization
Pharmacokinetics/Pharmacodynamics



Onufrak NJ, et al. Clin Ther. 2016 Sep;38(9):1930-47. doi: 10.1016/j.clinthera.2016.06.015.

Antimicrobial Pharmacokinetics

What to consider:

- Bioavailability of PO drugs
- Protein Binding of drugs: free unbound drug can have effect
- Route of drug elimination
  - Changing clinical condition such as organ damage or critical illness can affect rate of drug elimination
- Site of infection: Ability of antibiotic to reach the targeted tissue; ability to maintain adequate concentrations

Onufrak NJ, et al. Clin Ther. 2016 Sep;38(9):1930-47. doi: 10.1016/j.clinthera.2016.06.015.

Pharmacokinetic considerations by infection site

Infection Site	Pharmacokinetic Alteration	Potential Change to Dosing Regimen
Blood	Expanded Vd, enhanced CL	Provision of LD, increase frequency
Lung	Impaired permeability	Increase dose
Soft tissue	Contingent on body composition, comorbidities	Increase dose in obesity
Bone	Impaired permeability	Increase dose, duration of therapy
CNS	Impaired permeability	Maximal dose

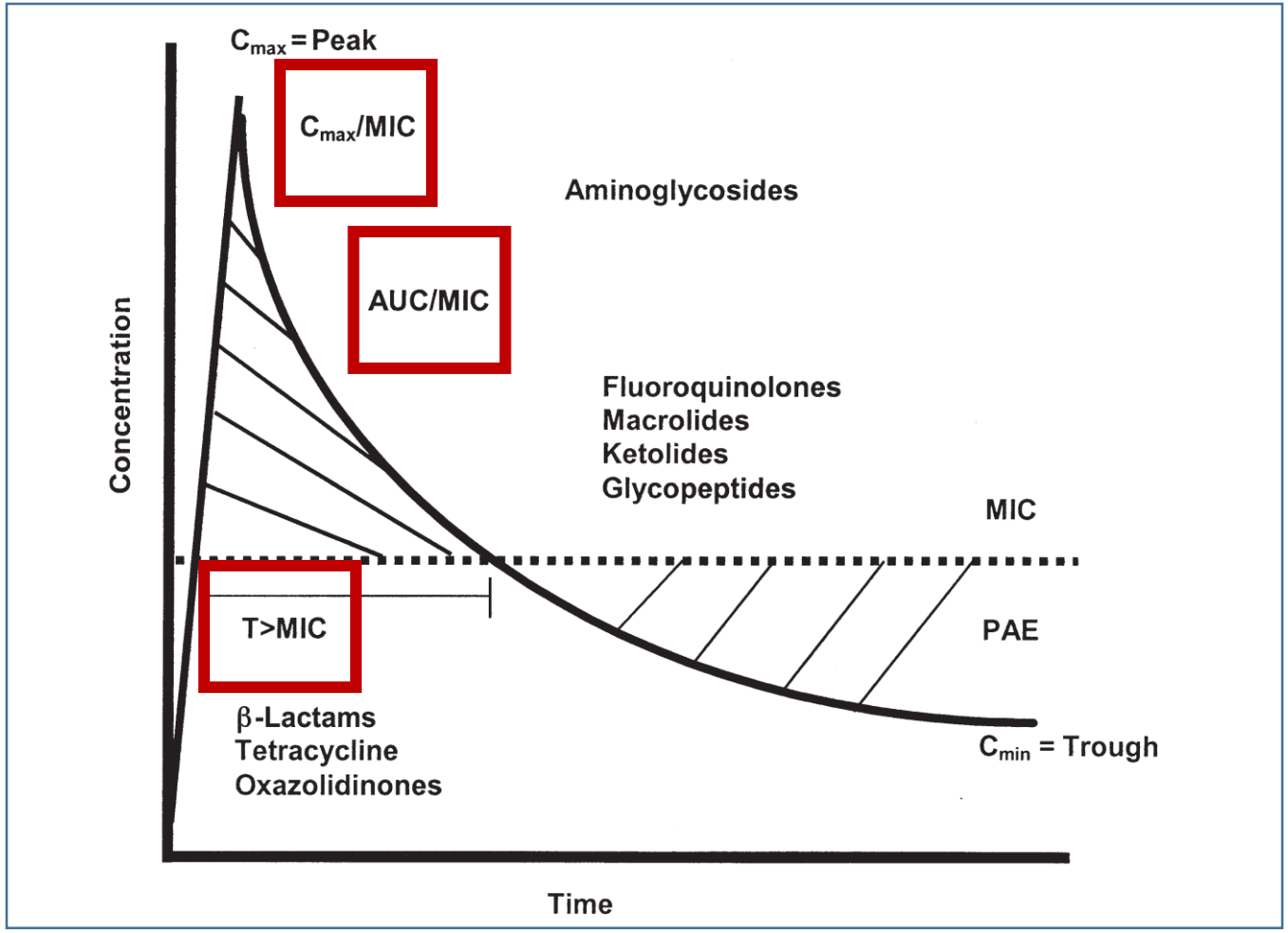
Onufrak NJ, et al. Clin Ther. 2016 Sep;38(9):1930-47. doi: 10.1016/j.clinthera.2016.06.015.

Pharmacodynamic Considerations

- Antibiotic PD is the impact of the antibiotic on a targeted pathogen
- Complex relationship and affiliated with:
  - Susceptibility of pathogen to a given antibiotic - MIC
- Delivering an effective dose is more complex than simply giving dose found to be effective in clinical trials

Onufrak NJ, et al. Clin Ther. 2016 Sep;38(9):1930-47. doi: 10.1016/j.clinthera.2016.06.015.

Boils down to 3 PD targets



Rybak MJ. Pharmacodynamics: relation to antimicrobial resistance. Am J Infect Control. 2006 Jun;34(5 Suppl 1):S38-45; discussion S64-73

Pharmacodynamics

	Concentration dependent killing	Time dependent killing
Drug Class	Fluoroquinolones Aminoglycosides Metronidazole	β-lactam antibiotics
Goal of Regimen	Peak drug concentration Post antibiotic effect	Maximize exposure time
Parameters Correlating with Clinical Efficacy	C_{peak}/MIC, AUC/MIC	Time > MIC

Clinical applications of PD

- Knowledge of PDs of β-lactams can affect:
  - Susceptibility and resistance breakpoints
  - Select from multiple drugs which one are best for certain organisms
    - *S. pneumoniae*: (PO) amoxicillin>cefuroxime>cefpodoxime
    - *H. influenzae*: (PO) cefpodoxime>cefixime
- In critically ill patients, an extended infusion time for β-lactams can be used to increase the time the drug concentration is above the MIC
- Extended infusion used for β-lactams: carbapenems, zosyn, ceftazidime, cefepime
  - Decreased mortality rates in critically ill patients
  - Increased clinical cure rates

Craig WA. Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, glycopeptides, and linezolid. Infect Dis Clin North Am. 2003 Sep;17(3):479-501

PK/PD considerations to minimize emergence of resistance

- Relation of PK/PD is complex and driven by MIC
  - MIC affected by inherent and acquired resistance and mutation frequency
  - Mechanical factors (biofilm, inoculum effects, stationary growth phase) can affect PD attainment
- Goal: achieve optimal drug exposure
- Optimal PD targets for resistance prevention are 2-4x higher than PD targets for clinical success
- High drug concentration needed:
  - For chromosomal resistance, suboptimum treatment might allow outgrowth of resistance pathogens with more costly and less efficient resistance mutations, which could lead to fully resistant organisms.
  - Acquisition of plasmid-borne resistance is facilitated by suboptimum treatment because low antimicrobial conc often have only bacteriostatic effects.

zur Wiesch PA, Kouyos R, Engelstädter J et al. Population biological principles of drug-resistance evolution in infectious diseases. Lancet Infect Dis. 2011 Mar;11(3):236-47.

Interpretation of MIC values on a C&S report

Blood Culture Report		
+ *Staph aureus*	Interpretation	MIC
Clindamycin	≤0.5	S (D-Test Positive)
Erythromycin	≥8	R
Oxacillin	≤4	S
Penicillin	≥0.5	R
Rifampin	≤0.5	S
Tetracycline	≤1	S
SMX/TMP	≤10	S
Vancomycin	1	S

Urine Culture- *E. coli*

Urine Culture Report		
+ *E. Coli*	Interpretation	MIC
Ampicillin	R	16
Ampicillin/sulbactam	S	2
Cefazolin	S	≤ 1
Ceftriaxone	S	≤ 1
Gentamicin	S	1
Ciprofloxacin	S	0.5
Nitrofurantoin	S	16
Trimethoprim/Sulfamethoxazole	S	≤ 2/38

Taking all these factors into consideration…

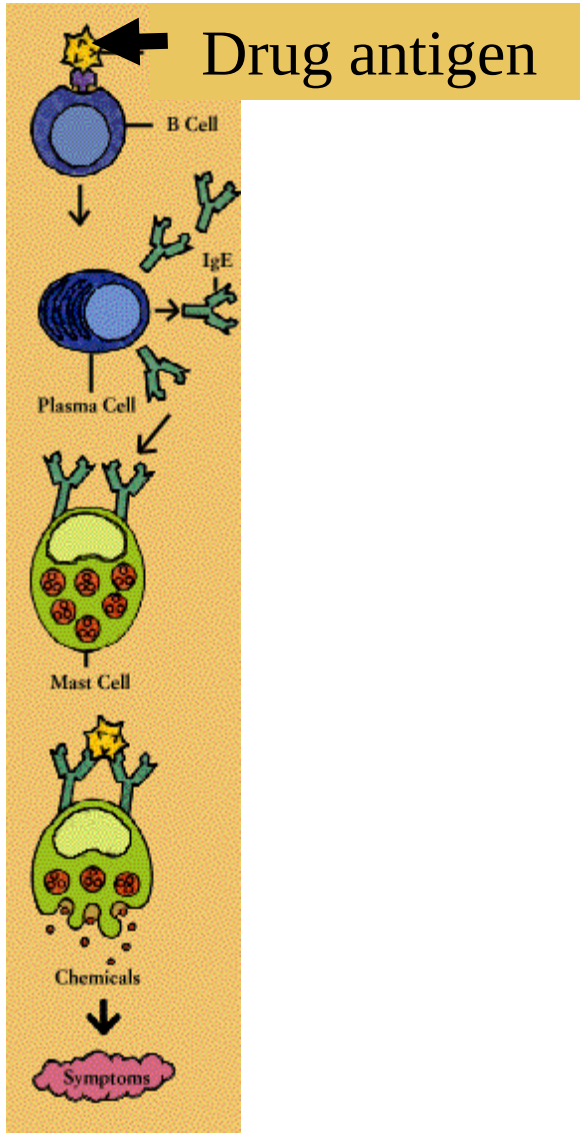
What do you choose?

LAC-USC Medical Center Empiric Antibiotics Recommendations

Infectious Diagnosis	Empiric first line recommendations
Cystitis	nitrofurantoin (Macrobid®)* 100mg PO bid x 5 days (avoid if CrCl < 30 ml/min) or cephalexin* 500mg PO bid x 3-5 days
Acute bacterial sinusitis	***98% are viral*** amoxicillin/clavulanate* 875/125mg PO bid x5 days
Community-acquired pneumonia	azithromycin 500mg PO x 1 day then 250mg PO x4 days
Cellulitis (No pus)	cephalexin* 500mg PO qid x 5 days
Purulent skin and soft tissue infection	Drainage first then trimethoprim/sulfamethoxazole* 800/160mg 1-2 tabs PO bid if MRSA is suspected cephalexin 500mg PO QID
Diabetic foot infection	amoxicillin/clavulanate* 875/125mg PO bid x7-14 days +/- trimethoprim/sulfamethoxazole* 1 DS tab PO bid

What to do if patient reports Penicillin Allergy?

- Patients labeled as penicillin allergic more likely to be treated with non-first line therapies, ↑ medical costs, ↑ LOS, ↑ complications like VRE or *C difficile* infections
- True penicillin (PCN) allergy is rare: 1-5 per 10,000 cases of PCN therapy
- 80% - 90% of pts who report a PCN allergy are NOT truly allergic to the drug, when assessed by skin testing
- In patients found to have PCN allergy, frequency of positive result on skin testing decreases by 10% per year of avoidance.
  - → 100% of patients are expected to test negative for penicillin allergy by 10 years after their reaction
- Common Types of PCN Reactions:
  - Immediate (Type I IgE mediated): < 1 hr after PCN administration
  - Sub-acute: 7-10 days after start of PCN treatment or 1-2 days after repeat therapy



Solensky R, et al. Ann Allergy Asthma Immunol. 2010 Oct;105(4):259-273.

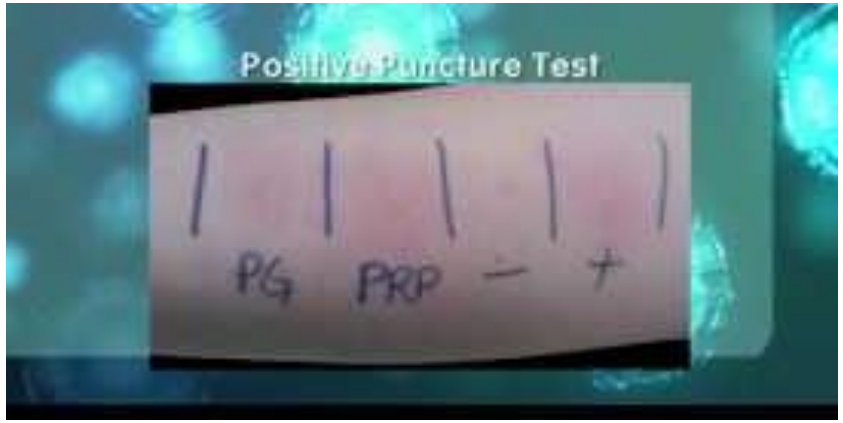
Cross-Reactivity with other β-lactam Antibiotics

- Cephalosporins
  - Frequency of allergic reactions w/in 24hrs of ceph admin for
    - pts w/Hx of PCN allergy and + skin test = 5.6%
      - If no alternative drug, Ceph desensitization may be required
    - pts w/Hx of PCN allergy and (-) skin test = 1.7%
      - Cephalosporin may be used
- Carbapenems
    - Low (1% to 10%)
    - pts w/ +skin test or hx of type I allergy to PCN
      - Graded challenge if a carbapenem is needed
- Aztreonam
  - Least cross-reactive with PCN

Solensky R, et al. Ann Allergy Asthma Immunol. 2010 Oct;105(4):259-273.

Penicillin Skin Testing

- Skin testing Procedure
  - Average time – 40 min; Cost ~ $17
  - Reagents:
    - Major determinant (benzyl penicilloyl, commercially available as PrePen)
    - Minor determinant - freshly diluted aqueous PCN G
  - Two steps: Prick test → Intradermal test
  - Result:
    - False negatives? → 3%
    - Positive – avoid penicillins and aminopenicillins
    - Negative – can give penicillin



Summary of Key Points

- ASPs are important for all healthcare settings
  - Primary goal: Improve patient outcomes
- ASPs have core members to implement protocols, however appropriate antimicrobial use is everyone's responsibility
  - Know the institution's antibiogram and empiric guideline recommendations
  - Re-evaluate patient reported penicillin allergy
  - Use optimal dosing for antibiotics using PK/PD concepts
- ASP targets will be customized to the institution and patient population
  - Protocols are evaluated and updated regularly