Antibiotic Rapid Review: Pearls and Pitfalls

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Conflict of Interest Disclosure

- I have no financial interest or contractual relationships with any commercial interest to disclose

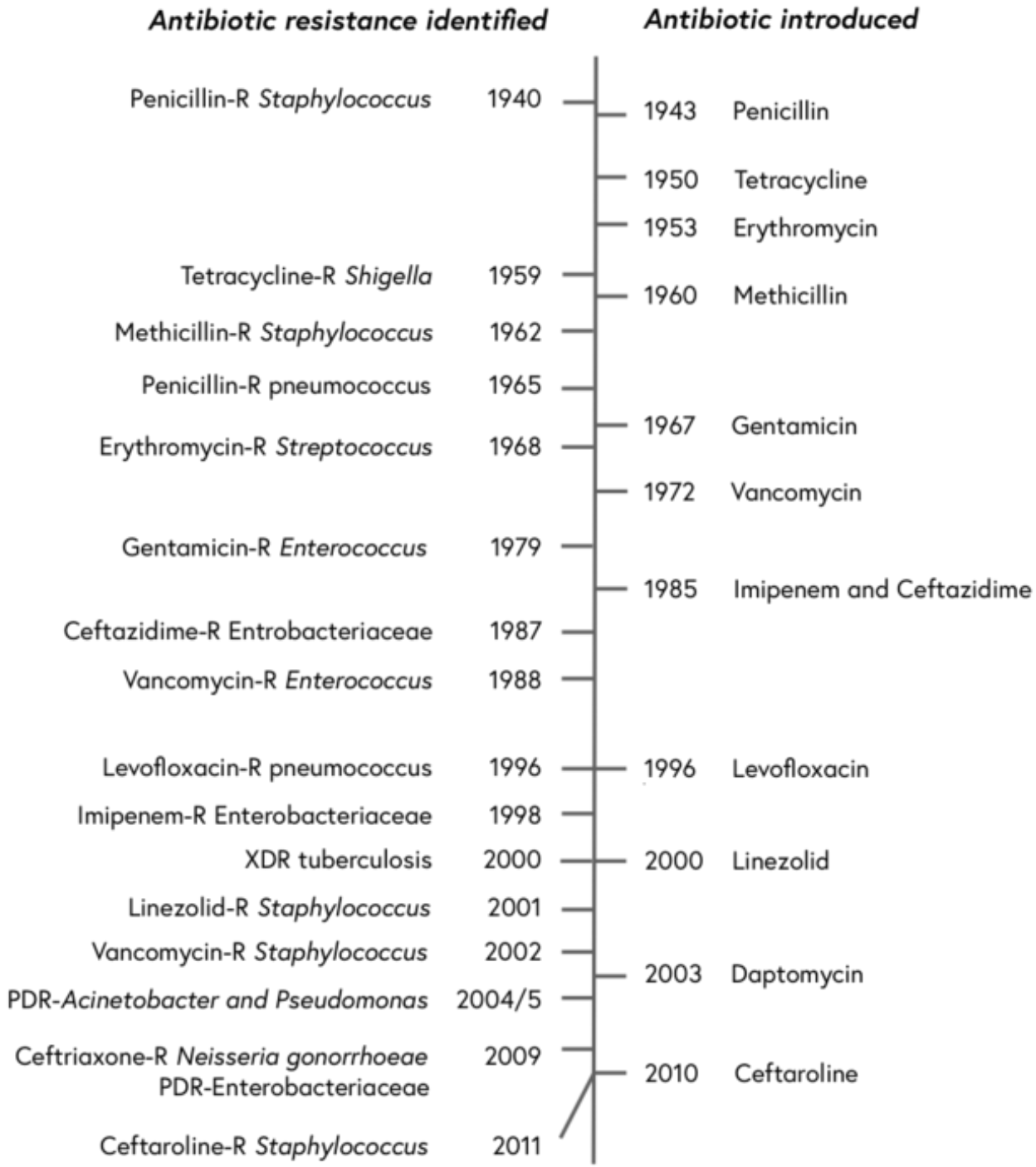
Objectives

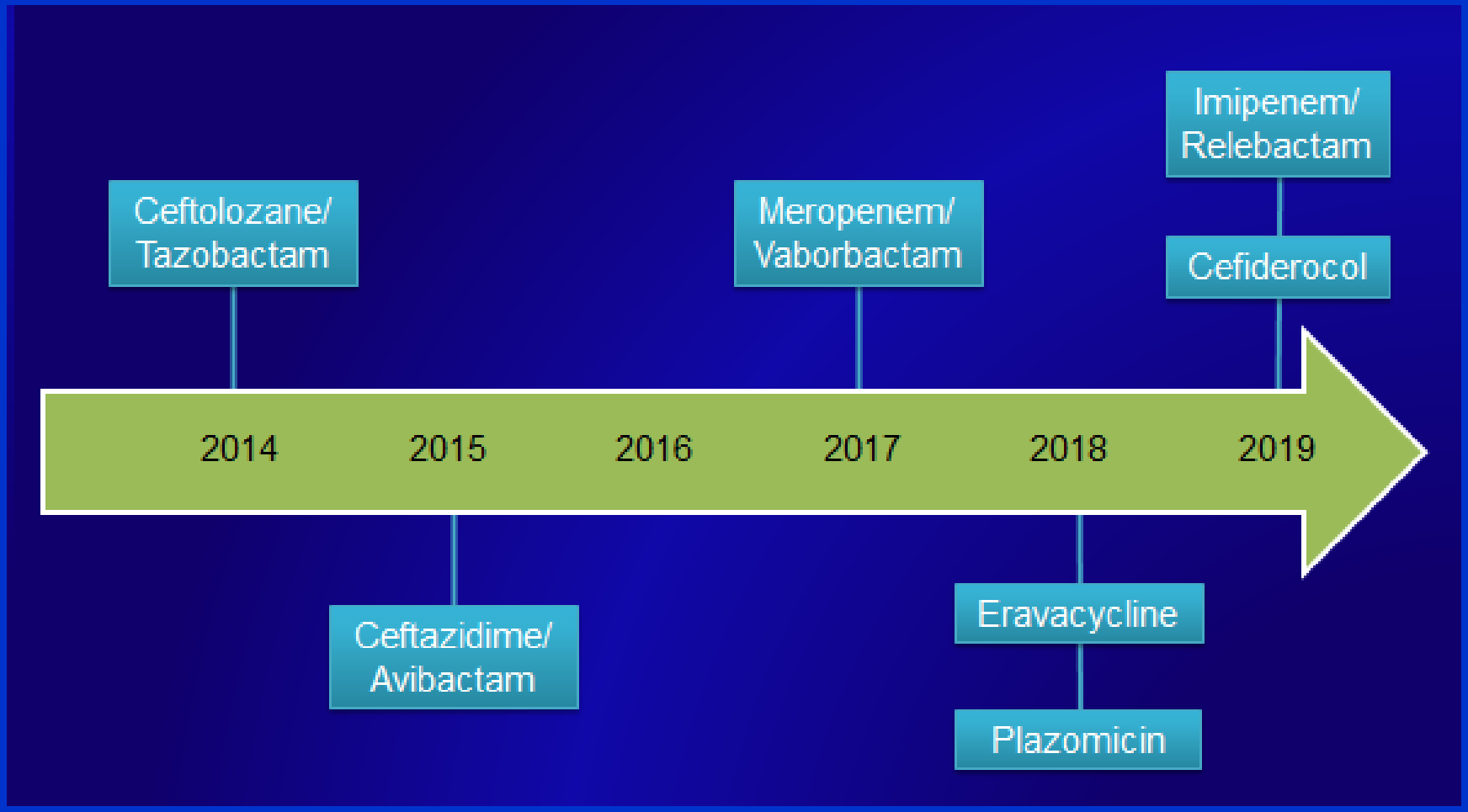
- General review of selected antimicrobials
- Discuss pearls and pitfalls related to antimicrobial use
- Understand how a better understanding of antibiotics leads to improved stewardship

Infectious Diseases and Human History

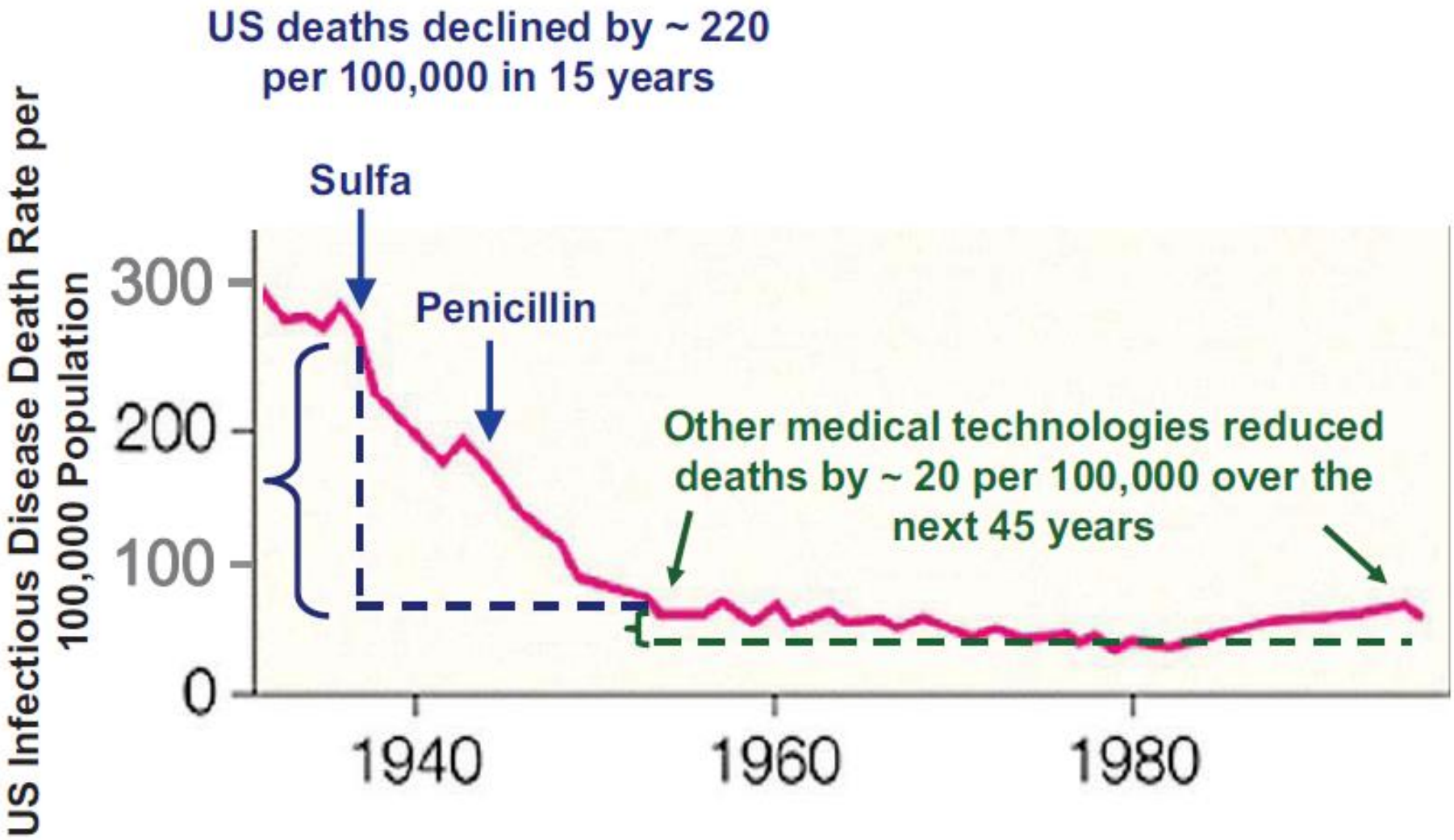
- Impact of infectious diseases on history cannot be underestimated
- Contributed to the collapse of empires / shaped history
  - Plague of Athens (430- 426 BCE)
  - Antonine (165 – 180 CE) and Justinian (541-549 CE) Plagues
  - Exposure of “New World” to various infectious diseases
  - Smallpox in the American revolution
  - Napoleon in Russia
  - 1918 flu
- Major historical figures killed by infections
  - Alexander
  - Pericles

1928 - *Penicillium chrysogenum*


Antibiotic resistance identified
Antibiotic introduced
Penicillin-R Staphylococcus
1940
1943
Penicillin
1950
Tetracycline
1953
Erythromycin
Tetracycline-R Shigella
1959
1960
Methicillin
Methicillin-R Staphylococcus
1962
Penicillin-R pneumococcus
1965
1967
Gentamicin
Erythromycin-R Streptococcus
1968
1972
Vancomycin
Gentamicin-R Enterococcus
1979
1985
Imipenem and Ceftazidime
Ceftazidime-R Entrobacteriaceae
1987
Vancomycin-R Enterococcus
1988
Levofloxacin-R pneumococcus
1996
1996
Levofloxacin
Imipenem-R Enterobacteriaceae
1998
XDR tuberculosis
2000
2000
Linezolid
Linezolid-R Staphylococcus
2001
Vancomycin-R Staphylococcus
2002
2003
Daptomycin
PDR-Acinetobacter and Pseudomonas
2004/5
Ceftriaxone-R Neisseria gonorrhoeae
PDR-Enterobacteriaceae
2009
2010
Ceftaroline
Ceftaroline-R Staphylococcus
2011


Ceftolozane/
Tazobactam
Meropenem/
Vaborbactam
Imipenem/
Relebactam
Cefiderocol
2014
2015
2016
2017
2018
2019
Ceftazidime/
Avibactam
Eravacycline
Plazomicin

Infectious Disease Mortality in the United States During the 20th Century



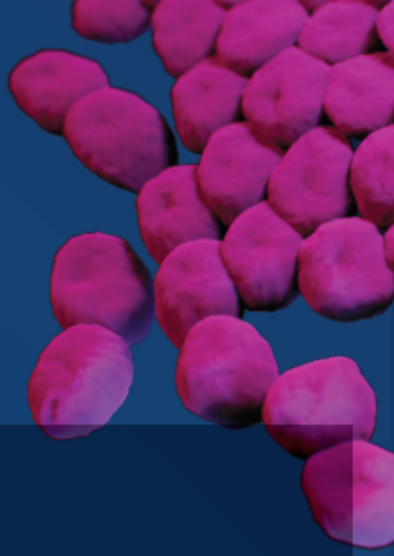
Modified from Armstrong, G. L. et al. JAMA 1999;281:61-6.

Antibiotics
A Double Edged Sword

Disadvantages

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

The Threat of Antibiotic Resistance in the United States



Antibiotic resistance—when germs (bacteria, fungi) develop the ability to defeat the antibiotics designed to kill them—is one of the greatest global health challenges of modern time.

New National Estimate*

Each year, antibiotic-resistant bacteria and fungi cause at least an estimated:

2,868,700 infections

35,900 deaths

+

***Clostridioides difficile* is related to antibiotic use and antibiotic resistance:**

223,900 cases

12,800 deaths

New Antibiotic Resistance Threats List

Updated urgent, serious, and concerning threats—totaling 18

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 (depending on the agent)
- The wrong antibiotic is given to treat an infection
  - Inappropriate for site, nonsusceptible at site, tissue penetration problem

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*)

Unimportant Factors

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

Antibiotic Resistance Potential

"High resistance potential" antibiotics → *antibiotics to avoid*

- **Ciprofloxacin**
  (*S. pneumoniae, P. aeruginosa*, ↑ MRSA)
- **TMP-SMX**
  (*S. pneumoniae, E. coli*)
- **Imipenem**
  (*P. aeruginosa*, ↑ MRSA)
- **Gentamicin/tobramycin**
  (*P. aeruginosa*)
- **Ceftazidime**
  (*P. aeruginosa*, ↑ MRSA)
- **Macrolides**
  (*S. pneumoniae*)

"Low resistance potential" antibiotics

IV

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

PO

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

Comparison of different antibiotics and the risk for community-associated *Clostridioides difficile* infect
A case-control study

Miller et al., 2023 | *Open Forum Infectious Diseases*

IDSA
Infectious Diseases Society of America

Study Population

Matched case-control study of patients with and without *Clostridioides difficile* infection (CDI), using a large database of commerical insurance claims.

Methods

Bayesian analysis used to estimate CDI risk associated with exposure to 27 different types of antibiotics within 30 days of infection. Comparison of time periods to capture antibiotic exposure (e.g., 90 days).

Results

Differentiated and ordered individual antibiotics in terms of their level of associated risk for CDI. Risk estimates varied across antibiotic types, classes and exposure windows.

CDI risk varies widely within and between classes of antibiotics; the individual type of antibiotic is important to consider for informing antibiotic stewardship tradeoffs with regard to CDI risk.

Open Forum Infectious Diseases https://doi.org/10.1093/ofid/ofad413

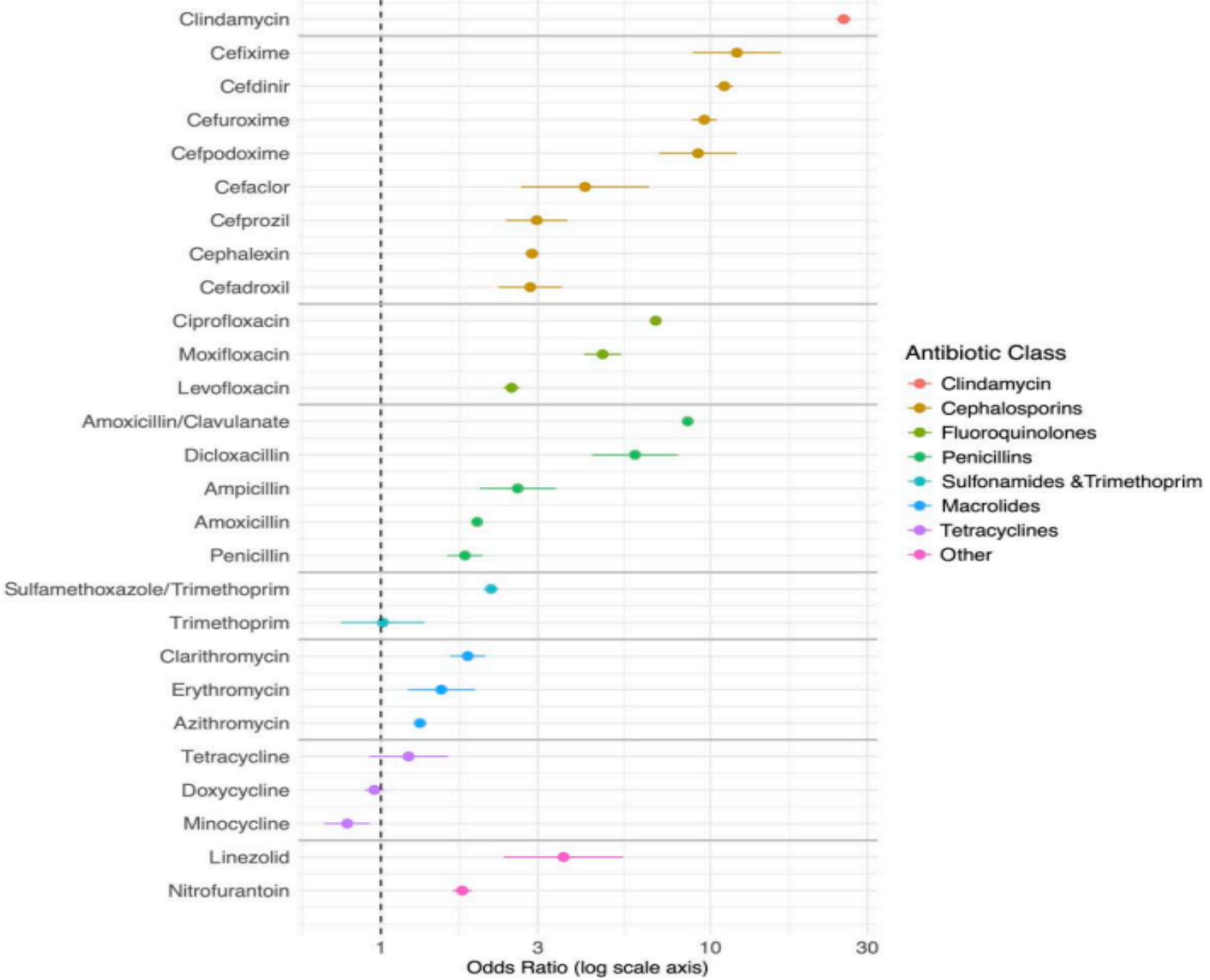


Figure 1. Visual comparison of effect estimates across antibiotic types, grouped by antibiotic class. Point estimates are depicted by the circle and 95% credible intervals by the line segments. Exact values can be found in Table 2.

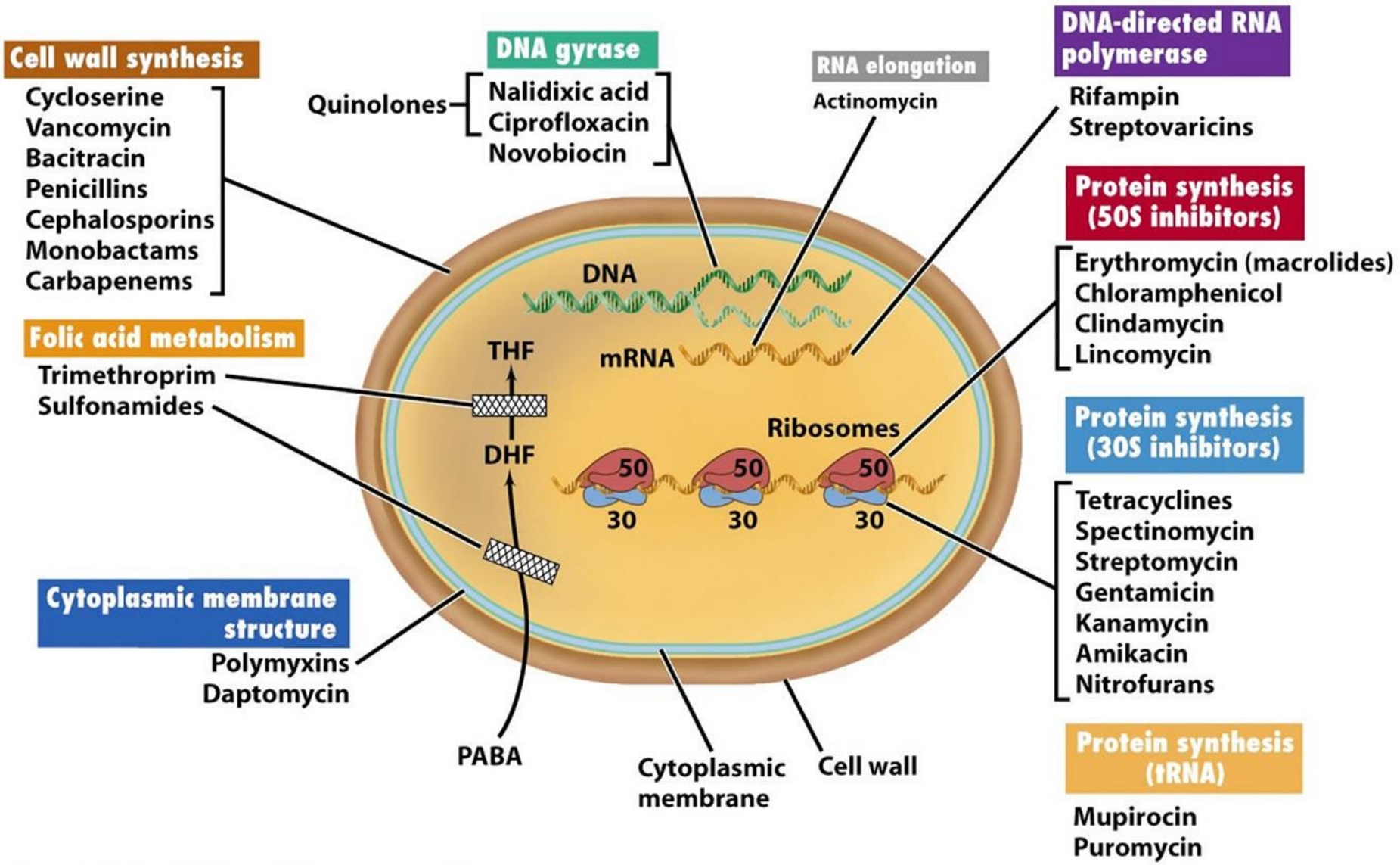
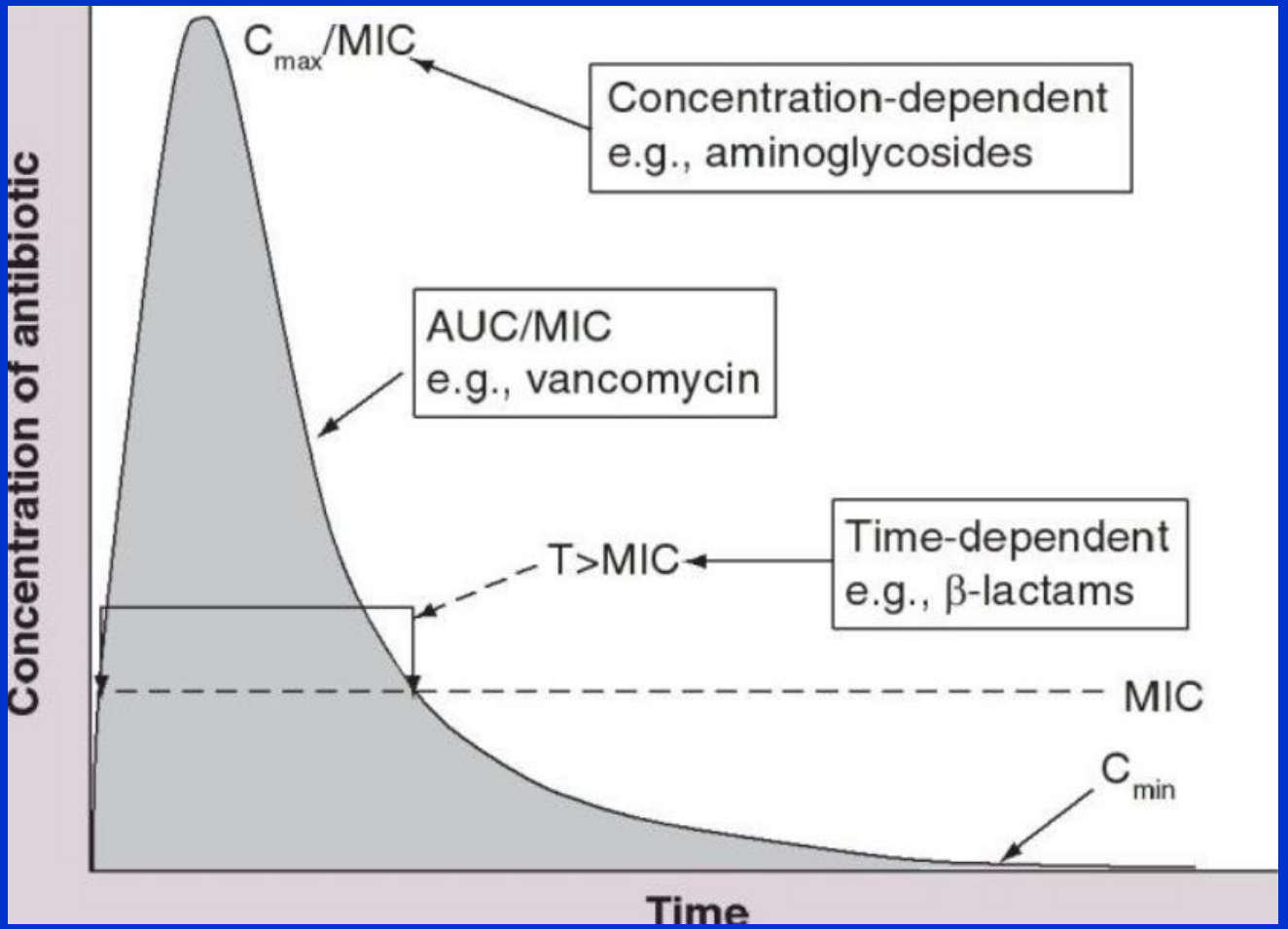


Figure 20-14 Brock Biology of Microorganisms 11/e

PK / PD Considerations in Antibiotic Dosing



Cunha CB, Cunha BA. Antibiotic Essentials (18 ed). Jaypee Publishing, New Delhi, 2024.

Penicillin

- **Route:** IV = G; PO = V or VK
- **Mode of elimination:** Renal

- **Hits**: Streptococci
  Gram negative diplococci (MC & GC)
  Oral anaerobes
  Syphilis

- **Misses**: MSSA/MRSA, ? *E. faecalis* (VSE), / *E. faecium* (VRE), GNBs, *B. fragilis*

- **Monotherapy:** Group A Streptococci (GAS), *S. pneumoniae*, syphilis
- **Oral PCN V/VK:** prophylaxis / therapy dental infections

- **SE**: Drug fever, drug rash, serum sickness

Ampicillin

- **Route: IV / PO**
- **Mode of elimination: Renal**
- **Hits**: Same as penicillin plus Enterococci (VSE), Listeria
- **Misses**: MSSA / MRSA, VRE, most GNBs, *B. fragilis*
- **Monotherapy:** Enterococcal endocarditis (usually ~~+ gent~~ / ceftriaxone), Listeria
- **SE**: Drug fever, drug rash
- **Pearls & Pitfalls (P&P):** No role for PO ampicillin, use PO amoxicillin instead
  - Ampicillin/sulbactam – may be active against MDR-Acinetobacter

Piperacillin-tazobactam

- **Route: IV**
- **Mode of elimination: Renal**

- **Hits**: Activity against most GNBs (K-E-S, *P. aeruginosa*), *B. fragilis*, MSSA, VSE

- **Misses**: MRSA, VRE, some resistant GNBs

- **Monotherapy:** IAIs, urosepsis, nosocomial pneumonia

- **SE**: Drug fever, drug rash

- **P&P:** Need 4.5 G IV q6h for nosocomial pneumonia when *P. aeruginosa* is suspected

Macrolides

- **Erythromycin**
- **Route: IV / PO**
- **Mode of elimination:** Hepatic

- **Hits:** GPCs (resistance in *S. pneumoniae*, MSSA), atypicals, some zoonotic pathogens

- **Misses:** Most GPCs due to increasing resistance. Most GNBs (except *P. multocida*)

- **Therapy:** topical eye therapy, ? GI motility

- **SE:** Diarrhea (not C. diff), QT prolongation

- **P&P:** Some failures in Legionnaire's disease. Suboptimal for Psittacosis

Macrolides

- **Azithromycin**
- **Route: IV / PO**
- **Mode of elimination: Hepatic**

- **Hits:** Erythro spectrum + H. flu, *Bordetella pertussis*

- **Misses:** Most GPCs due to increasing resistance

- **Therapy:** CAP with beta-lactam, AECB, Babesiosis (with atovaquone)

- **SE**: QT prolongation (far less than IV erythron), GI upset

Cephalosporins

- **1st generation (IV cefazolin; PO cephalexin)**
- **Route:** IV *HD / PO
- **Mode of elimination: Renal**

- **Hits:** Streptococci, MSSA, *E. coli*

- **Misses:** Listeria, VSE/VRE, MRSA, atypicals, *H. flu*, Enterobacter, Serratia, *P. aeruginosa, B. fragilis*

- **Monotherapy:** MSSA infections (not primary CNS), SSSIs, surgical ppx

- **SE**: Generally favorable / well tolerated

Cephalosporins

- **2nd generation (IV cefoxitin, cefotetan; PO cefuroxime)**
- **Route: IV / PO**
- **Mode of elimination: Renal**

- **Hits:** All from 1st gen plus *B. fragilis* (cefoxitin / cefotetan)

- **Misses:** Listeria, VSE/VRE, MRSA, atypicals, Enterobacter, Serratia, *P. aeruginosa*

- **Monotherapy:** mild to moderate IAI, DM foot infections (MSSA, GBS, GNBs, *B. fragilis*)

- **SE**: Cefotetan - disulfiram reaction from MTT side chain

Cephalosporins

- **3rd generation** (IV ceftriaxone, ceftazidime; PO cefpodoxime)
- **Route: IV *HD (ceftazidime) / PO**
- **Mode of elimination: Renal** (ceftriaxone is renal / hepatic, cefoperazone is hepatic)

- **Hits:** All from 1st gen plus GNBs (Klebsiella, Enterobacter, Serratia)

- **Misses:** Listeria, VRE (cefoperazone hits VSE), MRSA, atypicals, *B. fragilis*, *P. aeruginosa* except for cefoperazone & ceftazidime

- **Monotherapy:** Acute bacterial meningitis (excluding Listeria), CAP (typical), viridans Strep SBE, Lyme disease

- **Combination therapy:** IAI if used with *B. fragilis* drug (metronidazole)

- **SE**: Biliary sludging with ceftriaxone (reversible)

- P&P: Use meningeal dose for ABM (2 G IV q12h), ceftazidime has little MSSA activity
  - 1 G ceftriaxone OK for most infections other than CNS

Cephalosporins

- **4rd generation (IV cefepime)**
- **Route: IV *HD**
- **Mode of elimination: Renal**

- **Hits:** All from 3rd gen plus *P. aeruginosa*

- **Misses:** MRSA, VSE/VRE, atypicals, Listeria, *B. fragilis*

- **Monotherapy:** Febrile neutropenia, nosocomial PNA, *P. aeruginosa* infection

- **Combination therapy:** IAI if used with *B. fragilis* drug (metronidazole)

- **SE**: Seizures - usually in patients with renal insufficiency, high dose

Cephalosporins

- **5th generation (Anti-MRSA) cephalosporin - ceftaroline**
- **Route: IV**
- **Mode of elimination: Renal**

- **Hits:** MSSA, MRSA, VISA, CoNS, Streptococci, aerobic GNBs other than as noted below

- **Misses:** *P. aeruginosa*, Proteus, Enterobacter, Serratia, Acinetobacter, *B. cepacia, S. maltophilia, B. fragilis*, VSE/VRE

- **Monotherapy:** cSSSIs, MRSA / MSSA infection

- **SE**: Drug fever, drug rash, serum sickness

Carbapenems

- **Imipenem - cilastatin**
- **Route: IV**
- **Mode of elimination: Renal**

- **Hits:** GNBs including *P. aeruginosa*, MSSA, Streptococci, VSE, *B. fragilis*, some Nocardia

- **Misses:** MRSA, VRE, *S. maltophilia, B. cepacia*, Legionella / atypicals

- **Monotherapy:** ESBL infections, IAIs, DM foot infections

- **SE**: Seizures, particularly in those with renal failure
  Nausea if rapidly infused

Carbapenems

- **Meropenem**
- **Route: IV *HD**
- **Mode of elimination: Renal**

- **Hits:** GNBs including *P. aeruginosa*, MSSA, Streptococci, VSE, *B. fragilis*, Listeria

- **Misses:** MRSA, VRE, Legionella / atypicals

- **Monotherapy:** ESBL infections**,** IAIs, DM foot infections, nosocomial PNA, meningitis in PCN allergic patients

- **P&P:** No cross-reaction with PCN, safe to use if PCN allergic patients
  DDI with valproic acid

Supplement Figure 1. Beta-lactam Cross-Reactivity Chart

Antibiotic Ordered	Antibiotic Allergy: "Penicillin"	"Cephalosporin"	Amoxicillin/Amox/clav	Ampicillin/Amp/sulb	Aztreonam	Cefaclor	Cefazolin	Cefepime	Cefotaxime	Cefoxitin	Cefdinir	Ceftaroline	Ceftriaxone	Cefuroxime	Cephalexin	Ceftazidime/avibactam	Ceftolozane/tazobactam	Nafcillin	Penicillin G	Piperacillin/tazobactam
Amoxicillin/Amox/clav [16-21]	N	CPa,b		Nb	Yb	Na,b	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Nb	Yb	Yb	CPb	Nb	CPb
Ampicillin/Amp/sulb [16-21]	N	Cpa,b	Nb		Yb	Na,b	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Nb	Yb	Yb	CPb	Nb	CPb
Aztreonam [17, 19, 21]	Yb	Yb	Yb	Yb		Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Nb	CPb	Yb	Yb	Yb
Cefaclor [16-21]	N	N	Na,b	Na,b	Yb		Yb	Ya,b	Yb	Yb	Yb	Yb	UAa	UAa	Na,b	Yb	Yb	Yb	UAb	CPb
Cefazolin [16-21]	Ya,b	N	Yb	Yb	Yb	Yb		Yb	Yb	Ya,b	Yb	Yb	Ya,b	Ya,b	Yb	Yb	Yb	Yb	Yb	Yb
Cefepime [16-19, 21]	Ya,b	N	Yb	Yb	Yb	Ya,b	Yb		Nb	Yb	UAb	UAb	Na,b	Na,b	Yb	CPb	CPb	Yb	Yb	Yb
Cefotaxime [16-21]	Ya,b	N	Yb	Yb	Yb	Yb	Yb	Nb		UAb	UAb	UAb	Na,b	Na,b	Ya,b	Na,b	CPb	Yb	Yb	Yb
Cefoxitin [16-21]	UAb	N	Yb	Yb	Yb	Yb	Ya,b	Yb	UAb		Yb	Yb	UAb	Nb	Ya,b	Yb	Yb	Yb	Nb	Yb
Cefdinir [16-19, 21]	Yb	N	Yb	Yb	Yb	Yb	Yb	UAb	UAb	Yb		UAb	UAb	Yb	Yb	UAb	UAb	Yb	Yb	Yb
Ceftaroline [17-19, 21]	Yb	N	Yb	Yb	Yb	Yb	Yb	UAb	UAb	Yb	UAb		UAb	UAb	Yb	UAb	UAb	Yb	Yb	Yb
Ceftriaxone [16-21]	Ya,b	N	Yb	Yb	Yb	UAa	Ya,b	Na,b	Na,b	UAb	UAb	UAb		Na,b	UAa,b	Na,b	UAb	Yb	Yb	Yb
Cefuroxime [16-21]	Ya,b	N	Yb	Yb	Yb	UAa	Ya,b	Na,b	Na,b	Nb	Yb	UAb	Na,b		Ya,b	UAa,b	UAb	Yb	Yb	Yb
Cephalexin [16-21]	Na,b	N	Nb	Nb	Yb	Na,b	Yb	Yb	Ya,b	Ya,b	Yb	Yb	UAa,b	Ya,b		UAa	Yb	CPa	Nb	CPb
Ceftazidime/avibactam [16-21]	Ya,b	N	Yb	Yb	Nb	Yb	Yb	CPb	Na,b	Yb	UAb	UAb	Na,b	UAa,b	UAa		Nb	Yb	Yb	Yb
Ceftolozane/tazobactam [17, 19, 21]	Yb	N	Yb	Yb	CPb	Yb	Yb	CPb	CPb	Yb	UAb	UAb	UAb	UAb	Yb	Nb		Yb	Yb	Nc
Ertapenem [18]	Ya,b	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb
Meropenem [18]	Ya,b	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb
Nafcillin [17, 19]	CPb	Yb	CPb	CPb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	CPa	Yb	Yb		CPb	CPb
Penicillin G [16-21]	N	CPb	Nb	Nb	Yb	UAb	Yb	Yb	Yb	Nb	Yb	Yb	Yb	Yb	Nb	Yb	Yb	CPb		CPb
Piperacillin/tazobactam [17-19]	N	UA	CPb	CPb	Yb	CPb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	CPb	Yb	Nc	CPb	CPb	

[a]Comparison data in beta-lactam allergic patients; [b]Side chain extrapolation of beta-lactam antibiotic; [c]Extrapolation of beta-lactamase inhibitor

Y The order may be ordered/verified as long as any reaction other than type I-IV hypersensitivity reactions (HSRs). This includes general or non-specific allergy listings. For type I HSRs, a beta-lactam with a different side chain CAN be safely administered; however, prescribers should be notified to communicate this information and confirm the order. Avoid use in type II-IV HSRs.

UA "OK Unless Anaphylaxis" Agent may have limited or conflicting data or share a similar (not identical) side chain. Order/verify as long as the reaction is NOT listed as a type I-IV HSR.

N Should not be ordered/verified due to a higher likelihood of cross-reactivity. If ordered, the prescriber should be notified, and a different agent considered.

CP "Call Prescriber" The agent may have limited or conflicting data or share a similar (not identical) side chain. Risk/benefit should be evaluated.

Carbapenems

- **Ertapenem**
- **Route: IV *HD / IM**
- **Mode of elimination: Renal**
- **Hits:** GNBs, MSSA, Strep, *B. fragilis*
- **Misses:** P. aeruginosa, VSE/VRE, MRSA, Legionella / atypicals
- **Monotherapy:** IAIs, DM foot infections, ESBL infections
- **P&P:** Once a day dosing. (50% serum levels with IM dose)
  No cross-reaction with PCN, safe to use if PCN allergic pat

Lincosomides (Clindamycin)

- **Route: IV / PO**
- **Mode of elimination: Hepatic**

- **Hits:** MSSA, some MRSA, Streptococci, *S. pneumoniae*, *B. fragilis* (less reliable), Babesia

- **Misses:** VSE / VRE, aerobic GNBs

- **Monotherapy:** SSSI (MSSA, Strep), dental infections

- **Combination therapy**: Babesiosis (combo), adjunct in toxin mediated Staph / Strep infection

- **SE:** *C. difficile*

- **P&P:** May be useful in PCN allergy. Increased resistance and C. diff risk make it less helpful in adults.

  Interferes with toxin of GAS / Staph if susceptible

Aminoglycosides

- **Gentamicin, tobramycin, amikacin**
- **Route: IV**
- **Mode of elimination: Renal**

- **Hits:** Aerobic GNBs
- **Misses:** VSE / VRE, anaerobic GNBs, *B. fragilis*

- **Monotherapy:** GNB systemic infection / UTI

- **Combination therapy**: Staph aureus endocarditis (gent), Listeria ABM, IAIs if used with B. fragilis drug (metronidazole)

- **SE:** Ototoxicity (high, sustained peaks), nephrotoxicity (high, sustained trough levels). Enhanced if used with other nephrotoxic drugs

- **P&P:** Toxicity significantly reduced with once daily dosing.
- AGs suboptimal for pneumonia due to decreased activity at site (tissue hypoxia, WBC debris, local acidosis)

Monobactam

- **Aztreonam**
- **Route: IV**
- **Mode of elimination: Renal**

- **Hits:** Aerobic GNBs

- **Misses:** All Gram positives, *B. fragilis*

- **Monotherapy:** GNB systemic infection

- **Combination therapy**: IAIs if used with *B. fragilis* drug (metronidazole)

- **P&P:** Structurally similar to beta-lactams, but safe in PCN allergic patients
  Only cross reactivity is to ceftazidime

Trimethoprim-Sulfamethoxazole

- **Route: IV/PO**
- **Mode of elimination: Renal**

- **Hits:** Most GNBs, MSSA, MRSA, Pneumocystis, Nocardia, Toxoplasmosis, Listeria

- **Misses:** *P. aeruginosa, B. fragilis*, ? Streptococci

- **Monotherapy:** MSSA / MRSA, PCP, Nocardia, Toxoplasmosis, Listeria

- **SE:** TMP: Folate deficiency, hyperkalemia; SMX: SJS, hepatotoxicity, falsely elevates creatinine

- **P&P:** Active against Klebsiella in vitro but not in vivo.
  Trimethoprim alone is available PO

Glycopeptides

- **Vancomycin**
- **Route: IV *HD / PO**
- **Mode of elimination: Renal**

- **Hits:**
  - **PO:** *C. difficile*
  - **IV:** Gram positive organisms (no role in *C. diff* diarrhea / colitis)

- **Misses:** VRE, VRSA, GNBs, *B. fragilis*

- **Monotherapy: PO:** *C. difficile*; **IV:** GPC systemic infections

- **SE:** ? Nephrotoxicity. Vancomycin Flushing syndrome ("Red man")

- **P&P:** Use may increase VRE prevalence
  Monitoring, challenges with infusions makes alternatives preferable

Lipopeptides

- **Daptomycin**
- **Route: IV *HD**
- **Mode of elimination: Renal**

- **Hits:** Gram positive organisms (MRSA, VRE, Streptococci)

- **Misses:** GNBs, *B. fragilis*

- **Monotherapy:** Systemic GPC infection

- **SE:** myositis, eosinophilic pneumonia (rare)

- **P&P**: Prior exposure of Staph to vancomycin may thicken cell wall leading to daptomycin resistance

  Inactivated by surfactant

  Need higher doses for Enterococci

Oxazolidones

- **Linezolid / tedizolid**
- **Route: IV / PO**
- **Mode of elimination: Hepatic**

- **Hits:** MSSA, MRSA, CoNS, VSE, VRE, Streptococci

- **Misses:** All GNBs, *B. fragilis*

- **Monotherapy:** ORAL option for severe GPC infection

- **SE**: Dose related / reversible cytopenias (>2 weeks), peripheral neuropathy, serotonin syndrome, optic neuritis

- P&P: Toxin inhibition (like clindamycin)

Optimize Antibiotic Route
Myth: IV is always better than PO!

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

Why does it matter?

- IV antimicrobial therapy is not without complications
  - Phlebitis
  - Central line infection
  - DVT
- IV antimicrobial therapy may be more difficult for patients / family (may require staying at facility)
- IV antimicrobial therapy almost always more expensive / has greater environmental impact

Why does it matter?

- Good understanding of PK / PD should make you feel confident using PO therapy
- Well chosen PO therapy is just as effective as IV
- PO therapy should be routinely be considered as an alternative to IV therapy

Requirements of Oral Antibiotic Therapy

- Antibiotic factors:
  - ✓High degree of activity against the presumed / known pathogen
  - ✓High bioavailability that approximates serum / tissue concentrations
  - ✓Well tolerated, good safety profile
  - ✓Low resistance potential (bonus)

Cunha BA Oral Antibiotic Therapy of Serious Systemic Infections, Med Clin of N. America: vol 90, 2006.

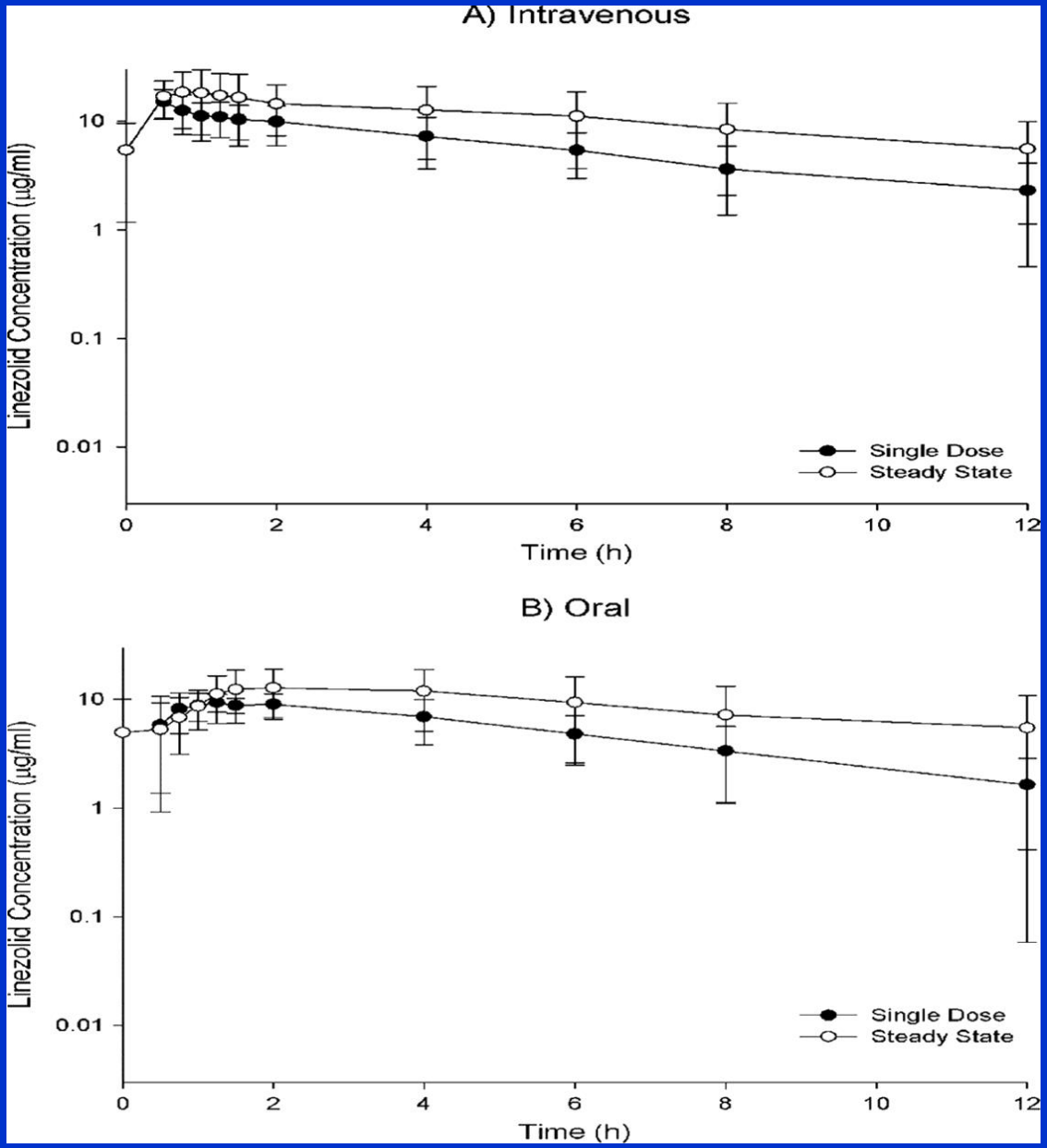
Requirements of Oral Antibiotic Therapy

- Host factors:
  - ✓ Therapeutic effect desired in >1 hour
  - ✓ Able to sufficiently absorb an oral antibiotic

Overview of Oral Antibiotic Therapy

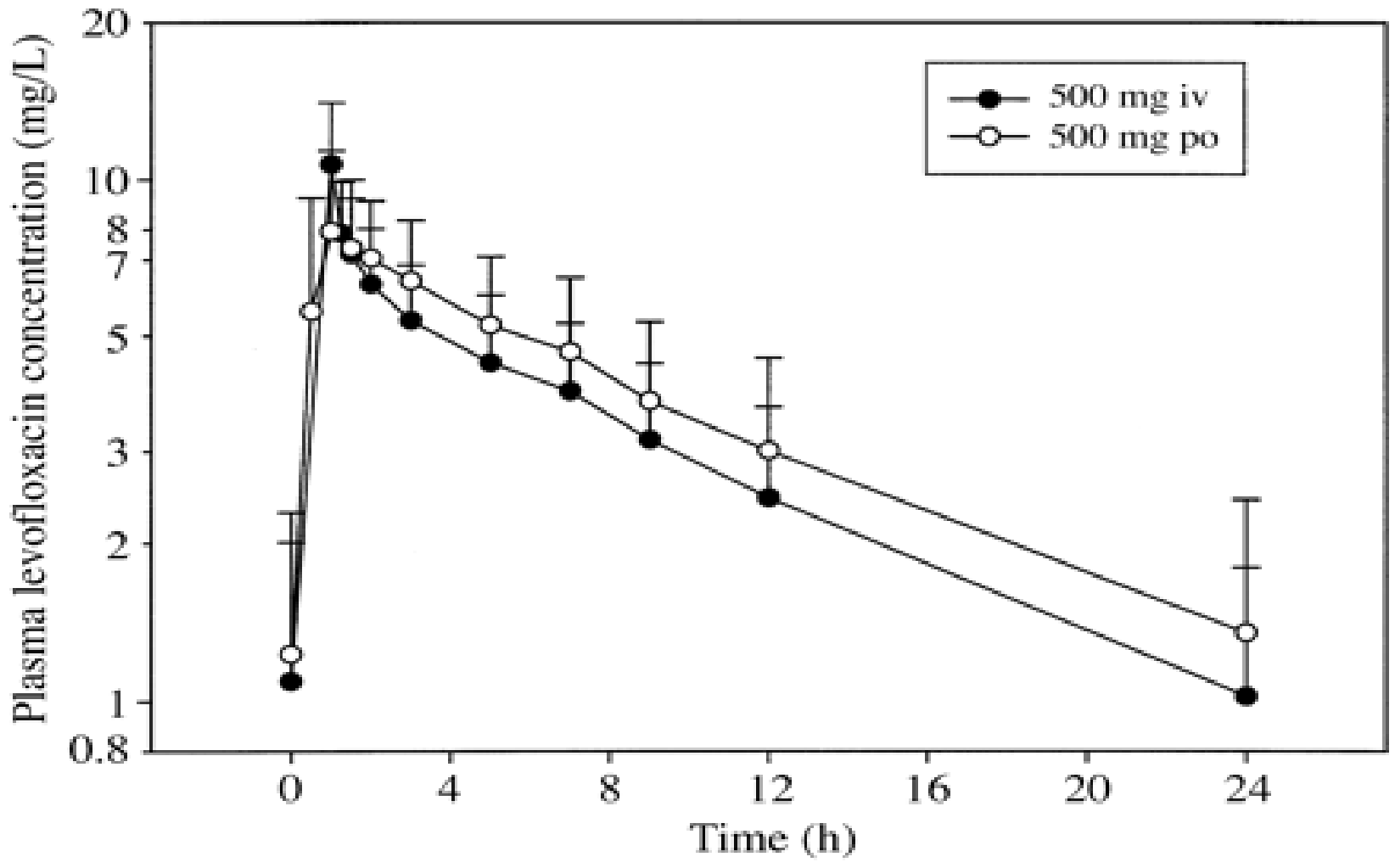
- Bioavailability is a key determinant
  - Low – not well absorbed → unsuitable for serious systemic infections (nitrofurantoin)
  - Good – blood / tissue levels not equal to IV but therapeutic concentration in excess of that needed for clinical effectiveness (cephalexin)
  - High - >90% absorption blood and tissue levels comparable or equal to IV (quinolones)

Mean and standard deviation intravenous (A) and oral (B) linezolid plasma concentrations over 12 h after the first dose and at steady state.



Rebecca A. Keel et al. Antimicrob. Agents Chemother. 2011; doi:10.1128/AAC.01797-10

Figure 1. Mean (±s.d.) steady-state levofloxacin plasma concentration–time profiles following iv and oral administration



Journal of Antimicrobial Chemotherapy, Volume 51, Issue 1, January 2003, Pages 101–106, https://doi.org/10.1093/jac/dkg035

Tetracyclines

- **Doxycycline**
- **Route: IV / PO**
- **Mode of elimination:** Hepatic

- **Hits:** MSSA, MRSA, many zoonotic / vector-borne pathogens, Actinomyces, atypicals, some *B. fragilis*, Chlamydia, syphilis

- **Misses:** Streptococci (except S. pneumoniae), Babesia, Pseudomonas (unless cystitis)

- **Monotherapy:** CAP, syphilis (PCN allergic), Lyme, Legionella, susceptible zoonoses, e.g. Q fever, plague, Brucella, etc., DoxyPEP, cystitis, prostatitis

- **SE:** GI upset, photosensitivity reaction

- **P&P:** Not active against Babesiosis
  Avoid concurrent Ca, Fe, Al, Mg administration

Urinary Spectrum of Oral Tetracyclines [a]

Parameters	Tetracycline	Doxycycline	Minocycline
Oral dose	500 mg	100 / 200 mg	100 mg
Serum levels	2 mcg/ml	4 / 8 mcg/ml	4 mcg/ml
Urine levels	~300 mcg/ml	~60 - 300 mcg/ml	~300 mcg/ml
Urinary spectrum	*E. coli* Klebsiella sp. Enterobacter sp. Indole + Proteus sp., *Pseudomonas aeruginosa*[b]		

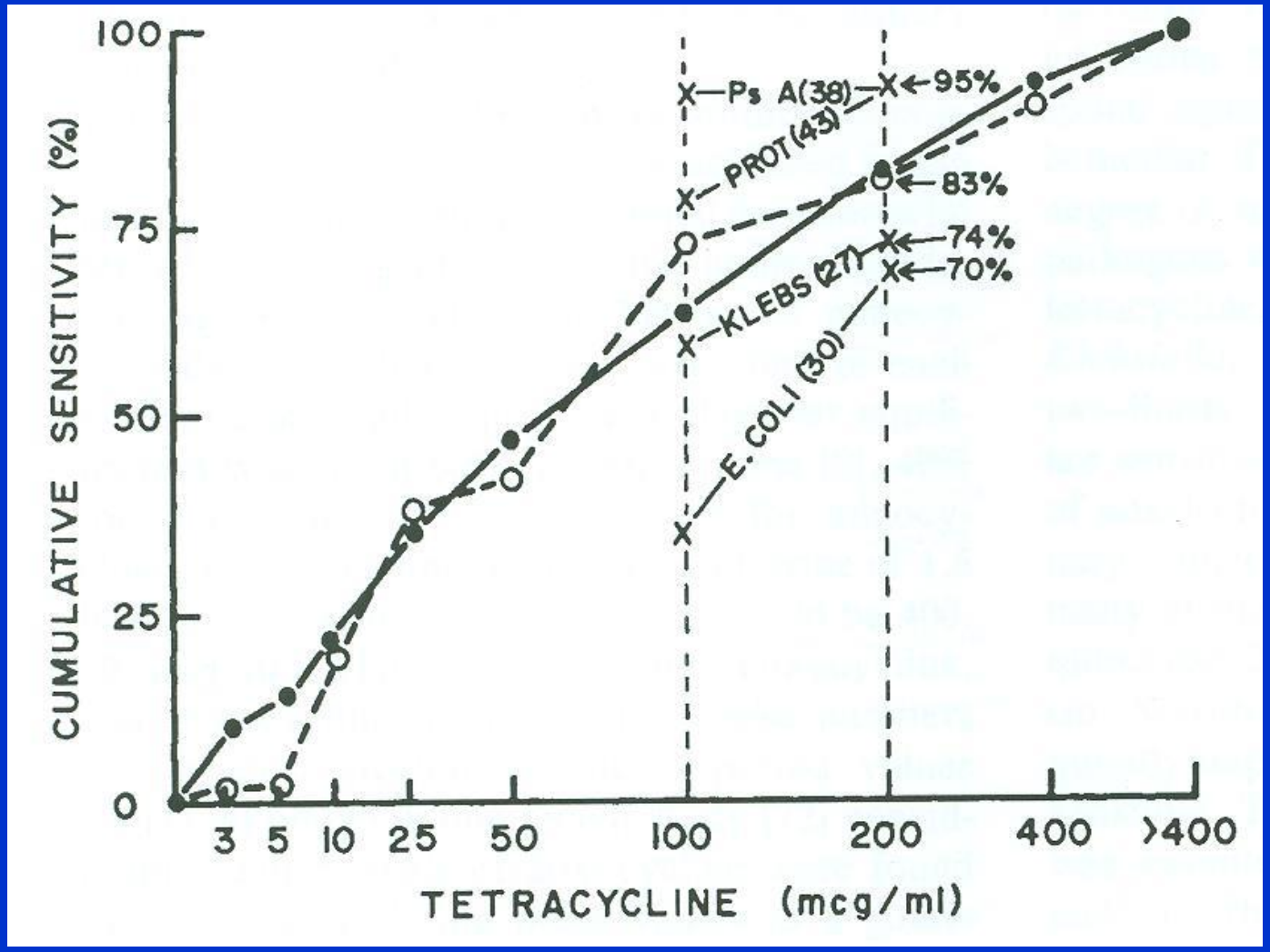
[a] With normal renal function

[b] MICs < 150 mcg/ml

White CR, Jodlowski TZ, Atkins DT, Holland NG. Successful Doxycycline Therapy in a Patient With Escherichia coli and Multidrug-Resistant Klebsiella pneumoniae Urinary Tract Infection. J Pharm Pract. 2017 Aug;30(4):464-467. doi: 10.1177/0897190016642362. Epub 2016 Apr 12. PMID: 27071978.

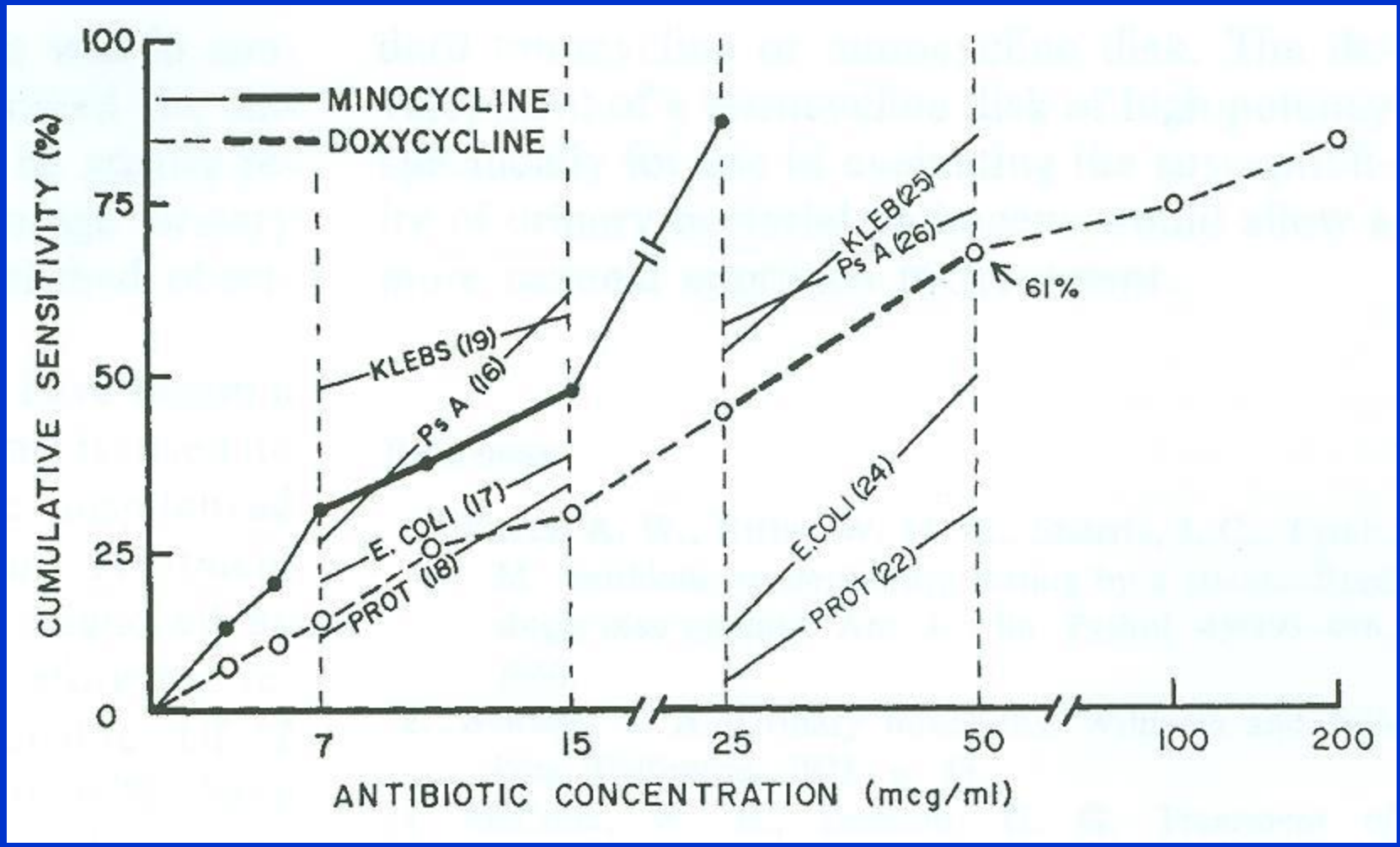
Cunha BA. Oral doxycycline for Non-systemic Urinary Tract Infections (UTIs) due to P. aeruginosa and other Gram Negative Uropathogens. Eur J Clin Microbiol Infect Dis 31:2865-2868, 2012.

Tetracyclines: Urinary Spectrum



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

Tetracyclines: Urinary Spectrum



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

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]		

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

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

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.

Tetracyclines

- **Minocycline**
- **Route: IV / PO**
- **Mode of elimination: Hepatic**

- **Hits:** MSSA, MRSA (more active than doxy), VRE, Nocardia, MDR-Acinetobacter, Actinomyces, some *B. fragilis*

- **Misses:** Streptococci (except *S. pneumoniae*)

- **Monotherapy:** MRSA, Acinetobacter, etc.

- **SE:** drug induced lupus, vertigo, skin discoloration with prolonged use (months)

- **P&P:** Better CSF penetration than doxy (50%)
  Tetra / doxy susceptibility does not predict mino activity
  More reliable than doxy for severe Staph infections

Tigecycline

- **Route: IV**
- **Mode of elimination: Hepatic**

- **Hits:** GPCs including MSSA / MRSA, VSE / VRE, most GNBs, MDR *K. pneumoniae*, Metallo-beta-lactamase, Acinetobacter, *B. fragilis, C. difficile*

- **Misses:** *P. aeruginosa*, Proteus, Providencia

- **Monotherapy:** IAIs, SSSI, *C. difficile*

- **SE:** GI upset, ?pancreatitis

- P&P: Once daily dosing better

  Can use higher doses in serious infection / UTI / bacteremia

Tigecycline

- PK / PD suggests package insert dosing (100mg IV x1, then 50mg BID) is suboptimal
- Half life is 27 hours after one dose, 42 hours after multiple doses
- Once daily dosing / higher dosing necessary for more severe infections. GI effect mitigated by infusing in larger volume / more slowly.

Loading dose x1, then maintenance daily dose	Peak serum concentration (Ug/mL)
100 mg / 50 mg	1.5
200 mg / 100 mg	3
400 mg / 200 mg	6

Metronidazole

- **Route: IV / PO**
- **Mode of elimination: Hepatic**

- **Hits:** *C. difficile*, *B. fragilis*, trichomonas, BV, amoeba
- **Misses:** Everything else

- **Monotherapy:** BV, Trichomonas

- **Combination therapy:** IAIs, DM foot infections / osteo in combination with a GNB drug (ceftriaxone, aztreonam, aminoglycoside), *C. difficile* colitis

- **SE**: Encephalopathy, seizures

- **P&P:** Suboptimal for *C. difficile* diarrhea
  1 G q24h (or 500 mg q12h) OK for most non-*C. difficile* infections

Nitrofurantoin

- **Route: PO**
- **Mode of elimination: Renal**

- **Hits:** GNB uropathogens (other than noted below) including ESBLs, CREs, VSE / VRE

- **Misses:** *P. aeruginosa*, Serratia, Proteus, GBS

- **Monotherapy:** Cystitis, CAUTI

- **SE**: Pneumonitis, pulmonary fibrosis, hepatitis

- **P&P:** For lower UTIs only
  Optimal effectiveness in CrCl >60 mL/min
  Usually still effective in CrCl 30-60 mL/min
  May not be effective in patients with CrCl <30 mL/min

Fosfomycin

- **Route: PO / IV (not in US)**
- **Mode of elimination: Renal**

- **Hits:** MDR GNB uropathogens including *P. aeruginosa*, Serratia, Proteus, VSE / VRE

- **Misses:** GBS, *S. maltophilia*

- **Monotherapy:** Cystitis, CAUTI, ? pyelonephritis

- **Combination therapy:** chronic bacterial prostatitis (with doxy / quinolone)

- **SE**: minimal, GI upset

- **P&P:** Excellent prostate concentrations (inflamed / noninflamed)
  May fail with chronic prostatitis in setting of prostatic calcifications

Quinolones

- **Ciprofloxacin (non-respiratory quinolone)**
- **Route: IV / PO**
- **Mode of elimination: Renal**

- **Hits:** GNBs (including P. aeruginosa), Strep spp., some VSE.

- **Misses:** Most MSSA, MRSA, S. pneumoniae, VRE, B. fragilis

- **Monotherapy:** UTIs, P. aeruginosa infections

- **Combination therapy:** IAI

- **SE:** Seizures, QT prolongation, tendon rupture, neuropathy, ?AAA

- **P&P**: Avoid concurrent Ca, Fe, Al, Mg administration (binds quinolones)

Avoid Ciprofloxacin for UTIs

Use Other Quinolones or Other Antibiotics

Problems with Ciprofloxacin

- "High resistance" potential → commonest cause of MDR GNR UTIs in community & hospital
- BID dosing
- Seizures with renal insufficiency/CNS abnormalities
- Use ↑ MRSA prevalence

Levofloxacin advantages*

- "Low resistance" potential
- QD dosing
- Low / no seizure risk
- Use doesn't ↑ MRSA prevalence

* moxifloxacin may be used instead of levofloxacin for pyelonephritis, prostatitis (but not cystitis, CAUTI)

Adapted from:
Cunha CB, Cunha BA. Antibiotic Essentials (18 ed). Jaypee Publishing, New Delhi, 2024.
Cunha BA. The fluoroquinolones for urinary tract infections: a review. Adv Ther. 11:277-96, 1994.

Quinolones

- **Levofloxacin**
- **Route: IV / PO**
- **Mode of elimination: Renal**

- **Hits:** MSSA, Streptococci (including S. pneumoniae), GNBs (including P. aeruginosa), some VSE, some zoonotic pathogens, atypicals

- **Misses:** MRSA, VSE / VRE, B. fragilis

- **Monotherapy:** CAP, nosocomial pneumonia, susceptible zoonoses

- **Combination therapy:** IAI

- **SE**: QT prolongation, tendon rupture (rare), neuropathy, ? AAA

- **P&P**: Use 750mg dose for Pseudomonas / nosocomial PNA

Quinolones

- **Moxifloxacin**
- **Route: IV / PO**
- **Mode of elimination: Hepatic**

- **Hits:** MSSA, Streptococci (including *S. pneumoniae*), GNBs, most VSE, atypicals, *B. fragilis*

- **Misses:** MRSA, P. aeruginosa

- **Monotherapy:** CAP, IAI (liver abscess), DM foot infections

- **SE**: QT prolongation, tendon rupture (rare), neuropathy, ? AAA

- **P&P**: Moxifloxacin has the best anti-VSE activity of FQs
  No need for dose adjustment in patients with renal insufficiency

"Antibiotic Failure" (apparent vs actual)

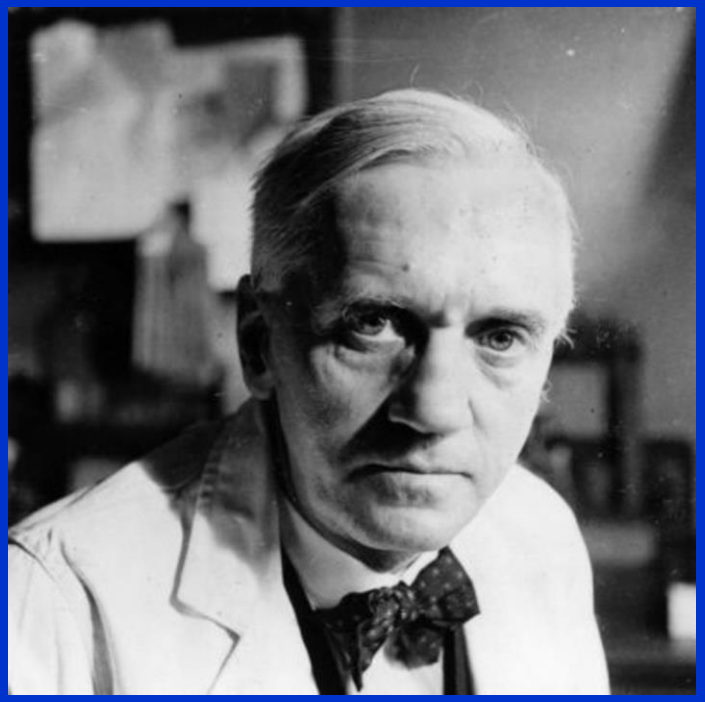
- Microbiologic Factors:
  - In vitro susceptibility but ineffective in vivo (quinolones may be reported as susceptible in MRSA isolates)
- Antibiotic Factors:
  - Inadequate coverage / spectrum
  - Inadequate antibiotic blood / tissue levels
  - Decreased antibiotic activity in tissue
  - Suboptimal activity at site

“Antibiotic Failure” (apparent vs actual)

- Antibiotic Penetration Problems:
  - Undrained abscess
  - Device related infections
  - Protected focus e.g., CSF
  - Organ hypoperfusion / diminished blood supply
- Noninfectious Disease:
  - Medical disorders mimicking infection e.g., SLE
  - Drug fever
- Antibiotic-unresponsive Infectious Diseases:
  - Viral or fungal infections

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

Thank you!