Principles of Antibiotic Therapy
Part 1

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UNIVERSITÀ DEGLI STUDI DI PADOVA

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Objectives

- Understand characteristics that impact underlying the selection of appropriate antimicrobial therapy
- Recognize common laboratory methods for bacterial pathogen identification and susceptibility testing
- Critically assess MIC testing methods and how results are reported through susceptibility breakpoints
- Identify common patient-specific factors that affect antibiotic selection
- Develop strategies for optimizing dosing and monitoring clinical response to antimicrobial therapy

These lessons will focus on antibacterials, but many concepts also apply to antiviral and antifungal medications. We will emphasize the differences in subsequent lectures

Outline

- How do you choose the correct antimicrobial for your patient?
- Patient factors that influence antibiotic selection
- Antimicrobial susceptibility testing and interpretation

Antimicrobial pharmacology is unique in medicine

Minimum inhibitory concentration (MIC)

- Antimicrobials are dosed on their ability to target a pathogen, not human receptors
- Antibiotic doses are administered in grams per day not mg or µg- *wide safety margin is important*
- Antibiotics must penetrate and be active in multiple body sites
- Antibiotic efficacy can decrease over time in individual patients or subsequent patients treated in the future
- We routinely alter doses based on MIC results and pharmacokinetics

“Antibiotic-like” therapy is not new…

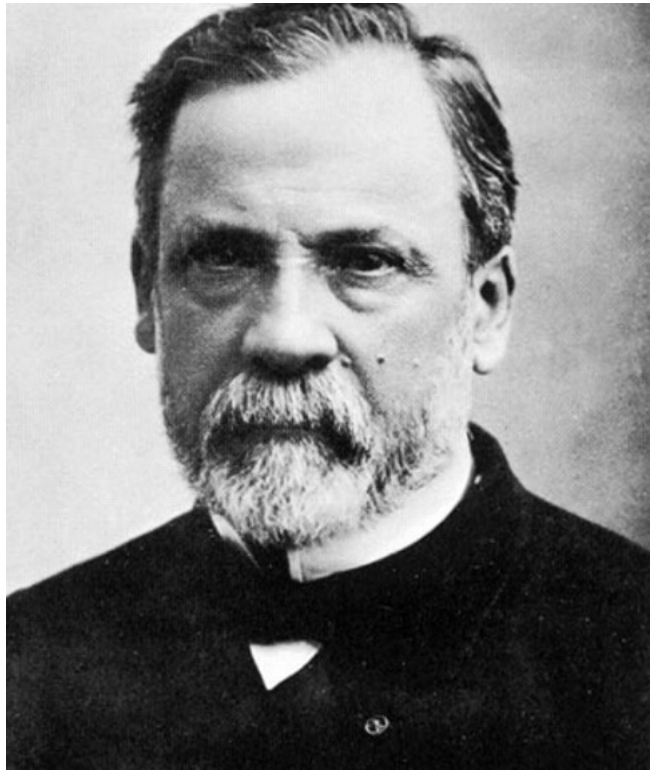
Chinese
Moldy tofu applied to skin infections

Egypt
moldy bread (Aish baladi) to treat skin lesions

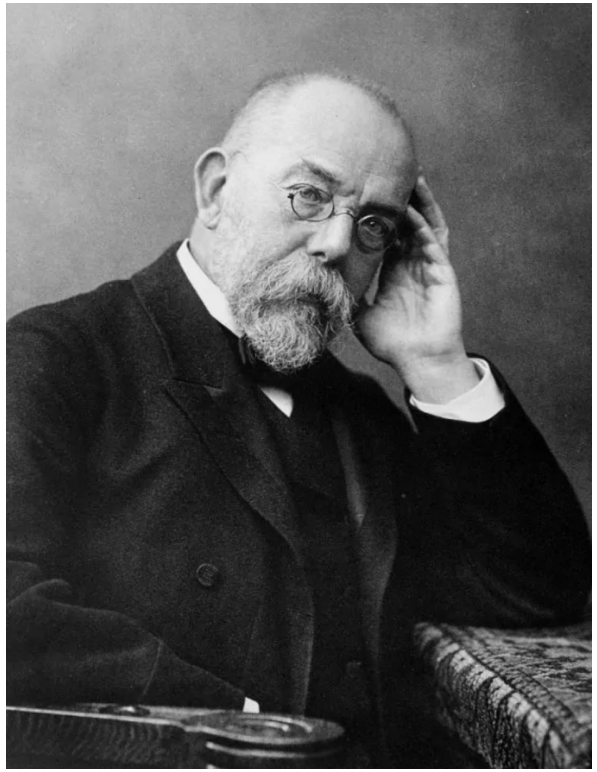
Greece (Hippocrates)
Wine, myrrh, inorganic salts in treatment of wounds

19th Century: Germ theory of disease

Antony van Leeuwenhoek (1632-1723)



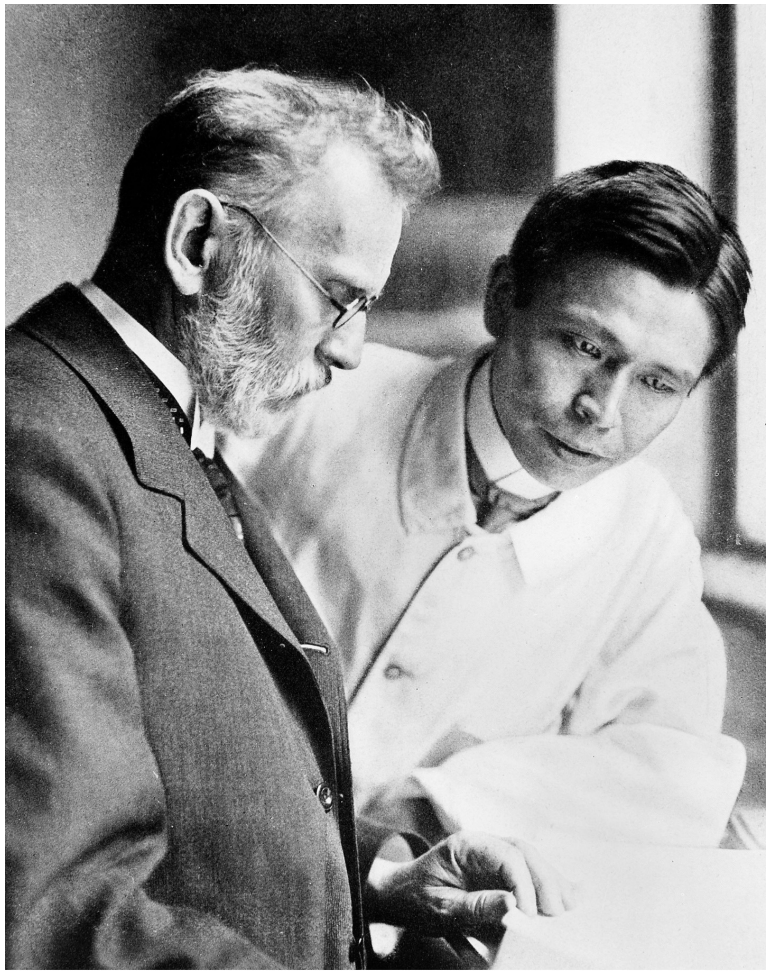
Louis Pasteur (1822-1895)



Robert Koch (1843-1910)

Arsphenamine (arsenic derivative) - Salvarsan 1909

The first treatment for syphilis (*Treponema pallidum*)



Paul Ehrlich (1854-1917) and
Sahachiro Hata (1873-1938)

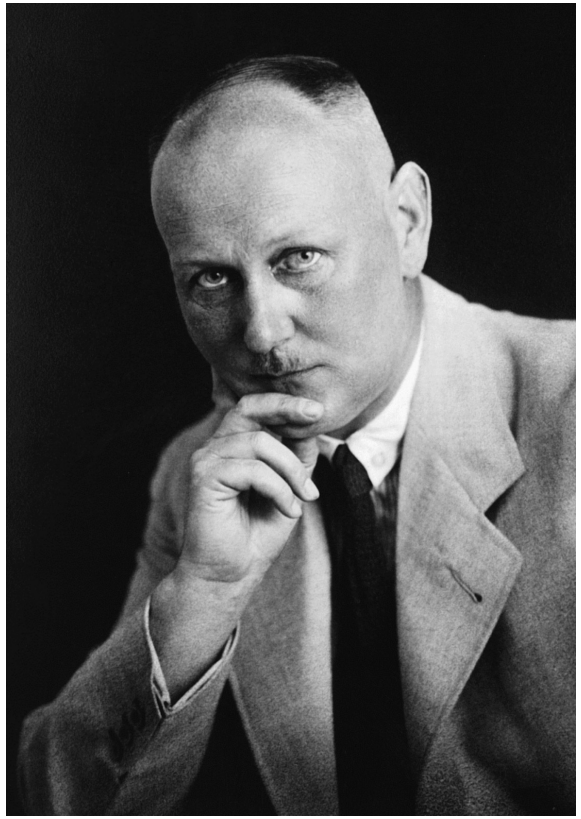
"Magic bullet"- chemotherapy

Arsphenamine - Salvarsan 1909

Side effects attributed to Salvarsan, including rashes, liver damage, and risks of life and limb, were thought to be caused by improper handling and administration of the relatively insoluble compound.

"The step from the laboratory to the patient's bedside ... is extraordinarily arduous and fraught with danger."
-Paul Erlich

Prontosil
First sulfa antibiotic (1932)



Gerhard Domagk
IG Farben
(Bayer Pharmaceuticals)

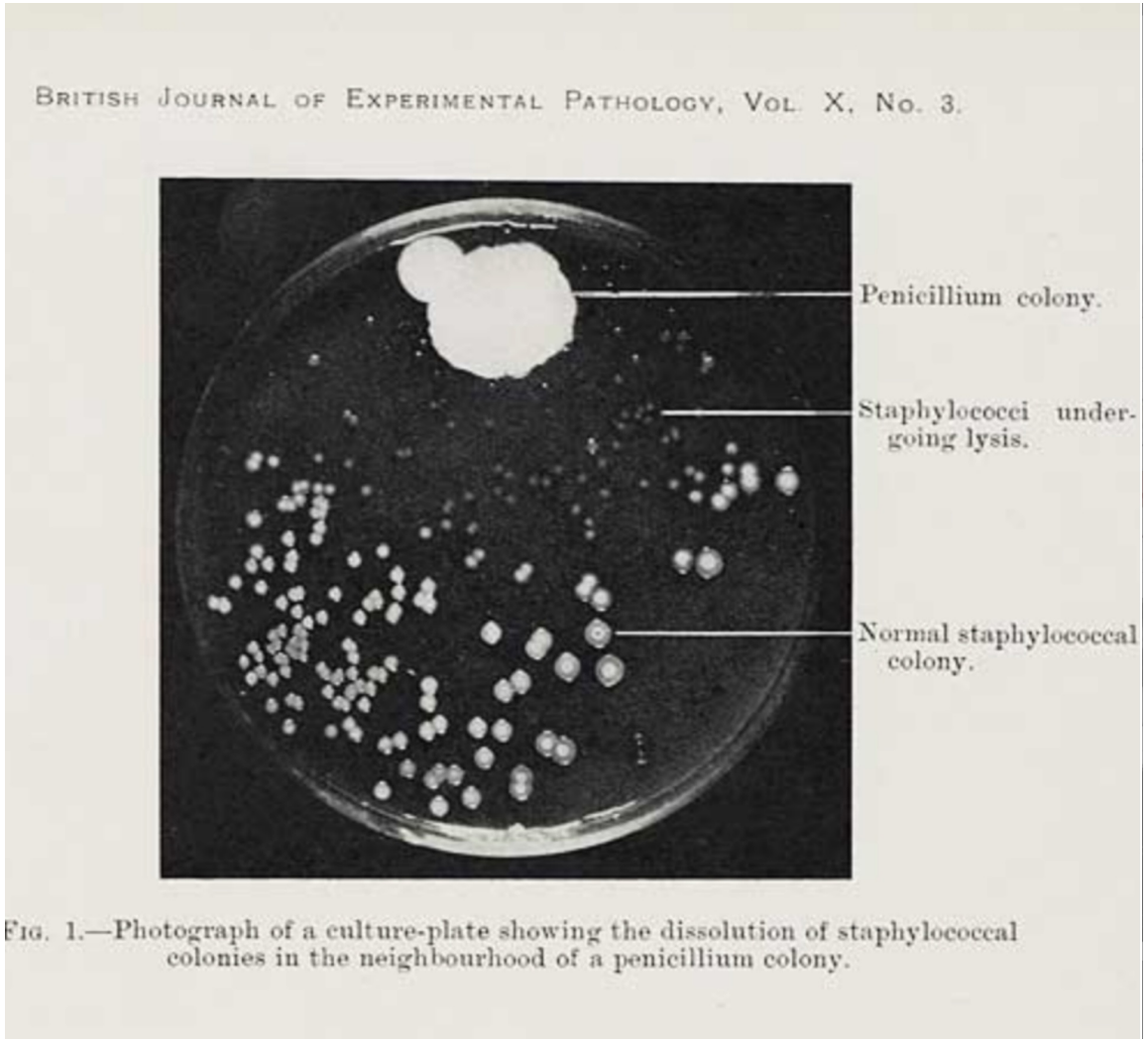
Prontosil metabolized to sulfanilamide *in vivo*

Among the early patients was Domagk's own 6 year old daughter, Hildegard, who had contracted a severe streptococcal cellulitis/sepsis from an accident with a sewing needle.

Utterly desperate when the doctor recommended amputation to save his daughter's life, Domagk treated Hildegard with Prontosil.

Hildegard recovered, but suffered a permanent reddish discoloration of her skin owing to the drug.

Penicillins: Modern antibiotic era



British J of Pathology 1928

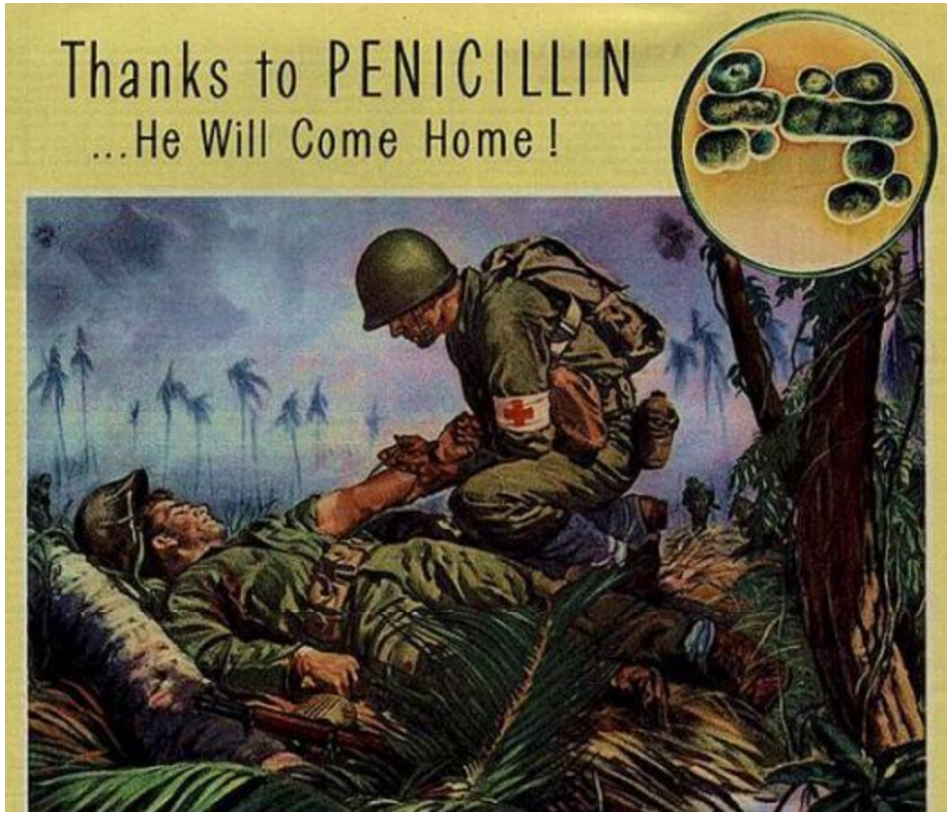
Sir Alexander Fleming (1881-1955)

Ernst Boris Chain (1906-1979)

Sir Howard Walter Florey (1898-1968)

1930s-40s

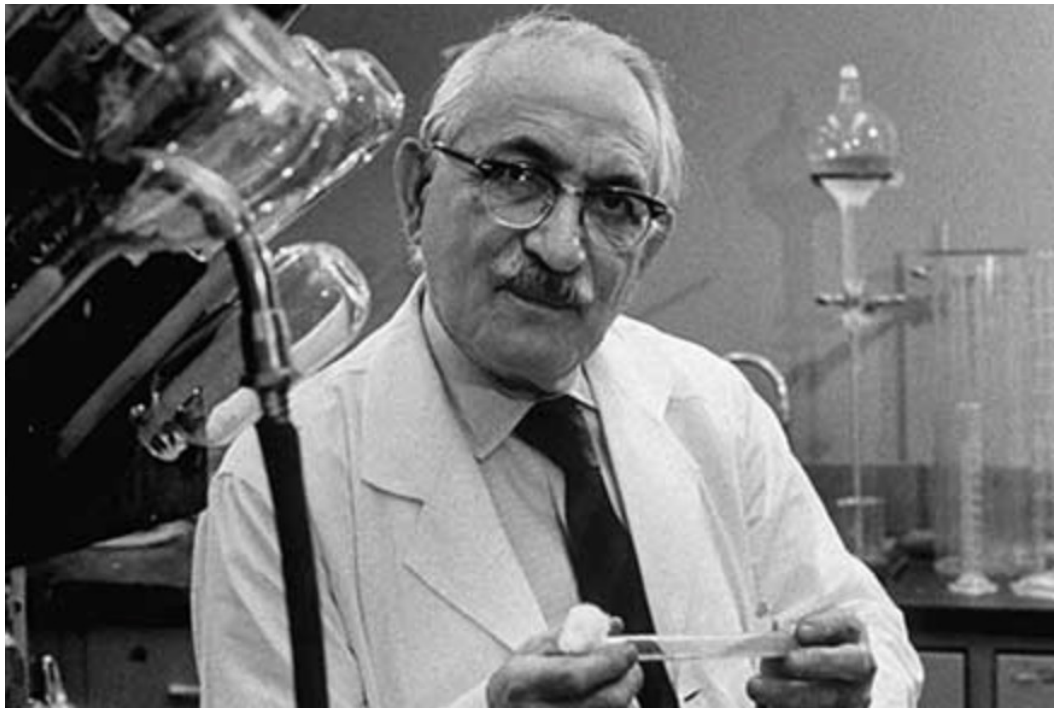
Fermentation of penicillins



In June of 1943 Mary Hunt, a lab assistant working in Peoria, Illinois, found a cantaloupe at a local market covered in mold with a “pretty, golden look.”

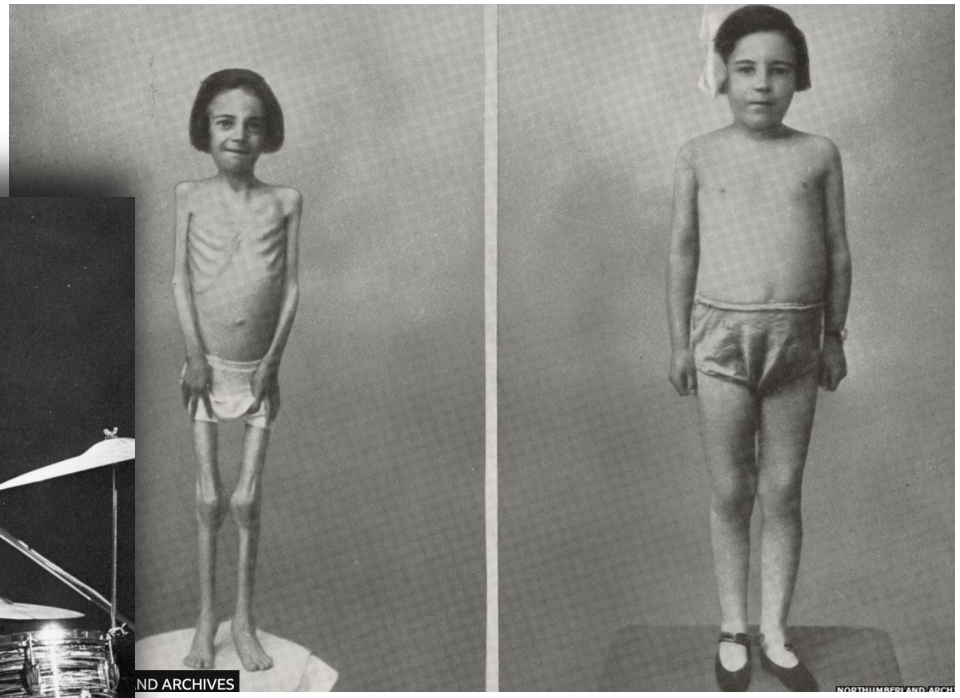
This mold turned out to be a highly productive strain of *Penicillium chrysogeum* and its discovery marked a turning point in the quest to mass produce penicillin.

Who coined the term “antibiotic”?



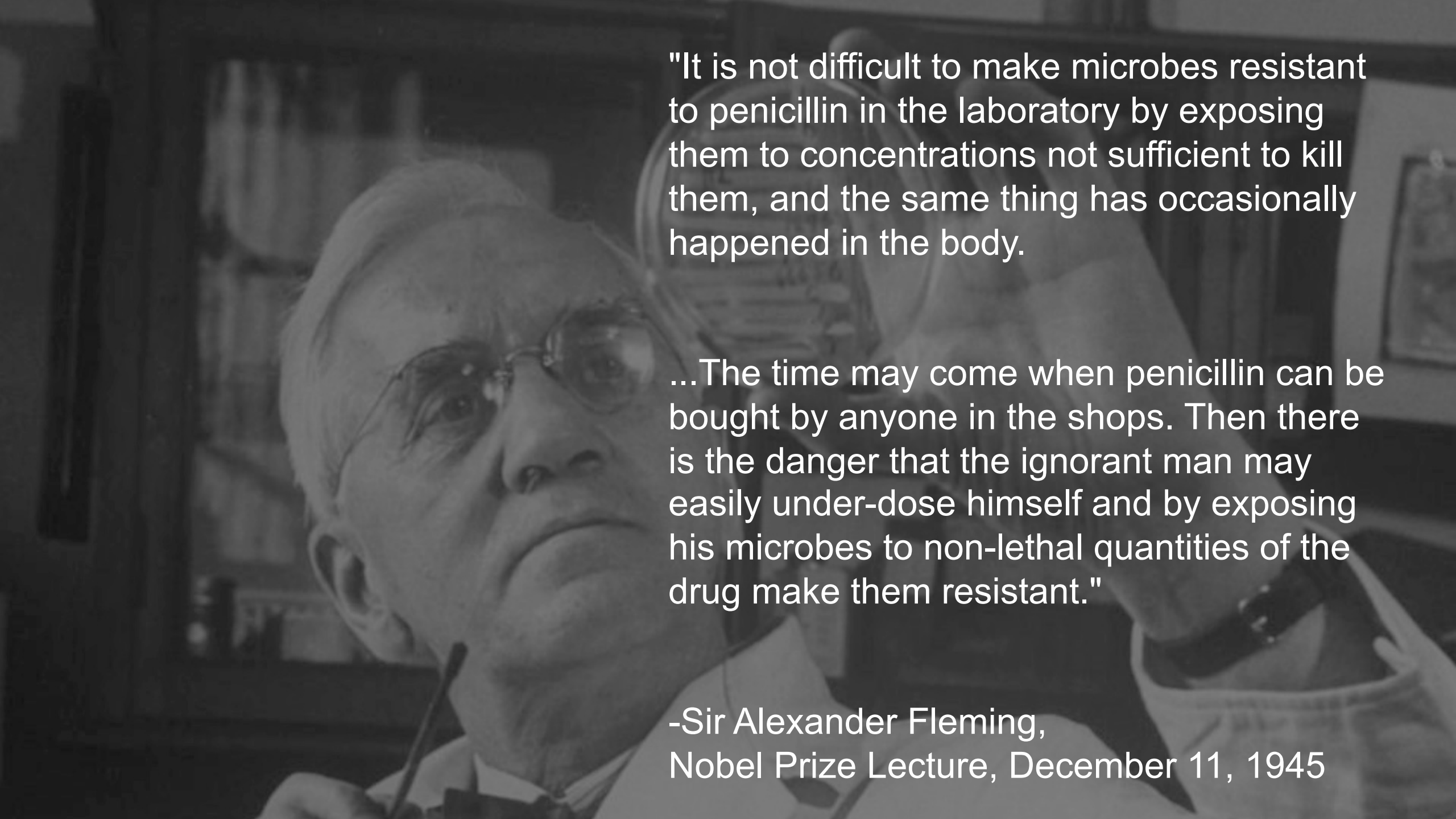
Selman Wakesman 1945 (streptomycin)
Photo: Rutgers University

TB sanatorium and streptomycin treatment



Nystatin- First Antifungal (1950)

Elizabeth Hazen (left) and Rachel Brown, 1955.
Photo: Smithsonian Collection

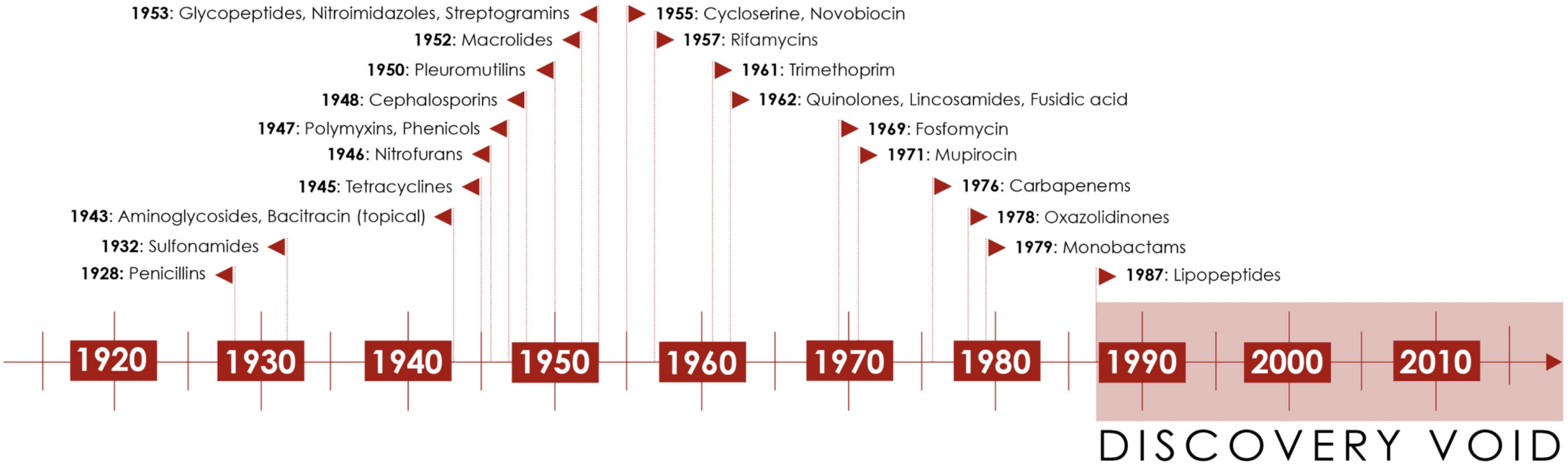


"It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body.

...The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily under-dose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."

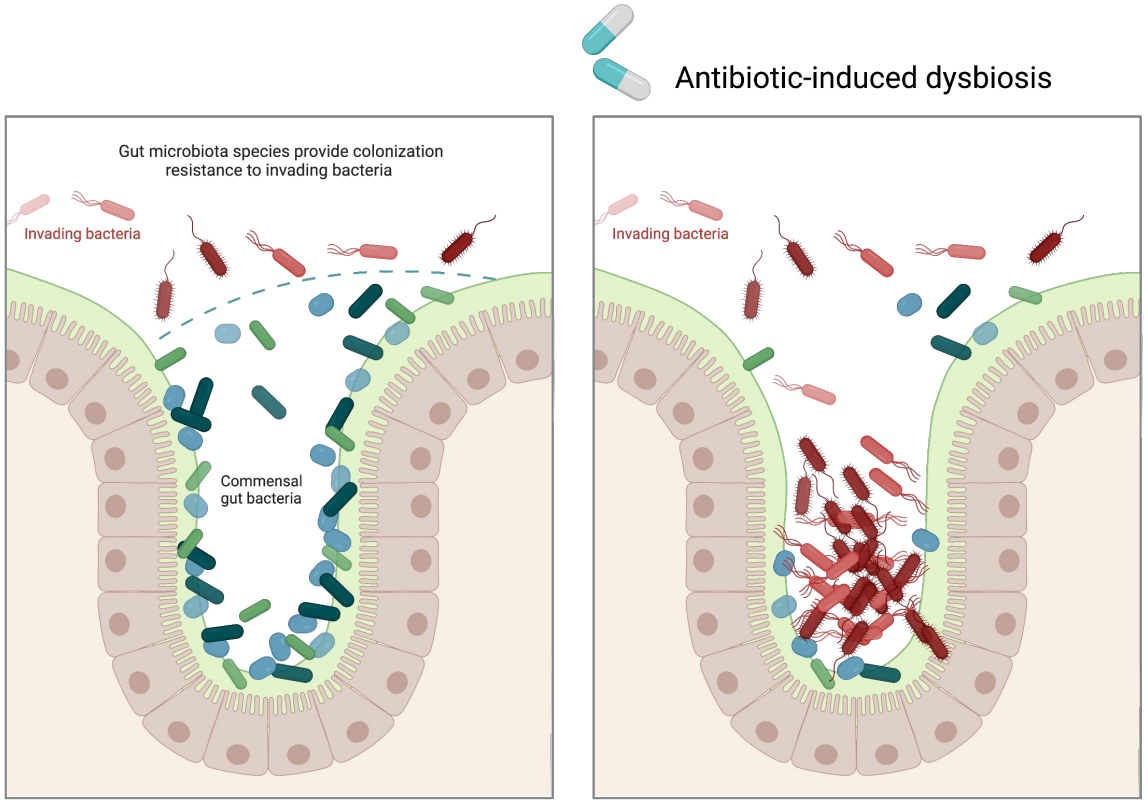
-Sir Alexander Fleming,
Nobel Prize Lecture, December 11, 1945

Antibiotic timeline



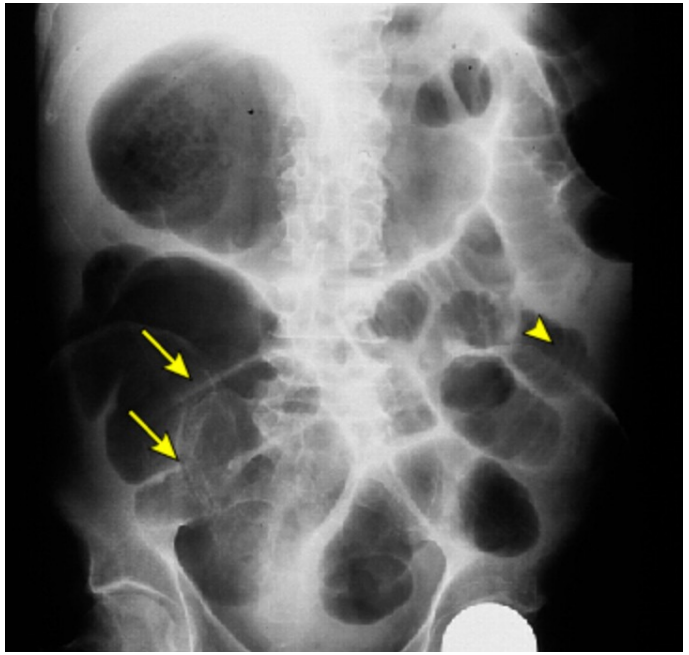
Source: www.react.org

Antibiotics: "Collateral damage”



Disruption of the gut microbiome,
Superinfections with resistant pathogens

Clostridium difficile colitis



4C’s of C. difficile

- Clin*damycin*
- Cephalosporins
- *Co-amoxicillin- clavulanate*
- Ciprofloxacin

Plain film of the abdomen from a patient with toxic megacolon associated with *Clostridioides* (formerly *Clostridium*) *difficile* infection. The large and small intestines are grossly dilated. Dilatation of the small bowel, which has the thin transverse folds of the valvulae conniventes (arrowhead), is seen best in the left lower quadrant. Large bowel dilatation occupies most of the right lower quadrant and has characteristic thick haustral markings that do not extend across the entire lumen (arrows).

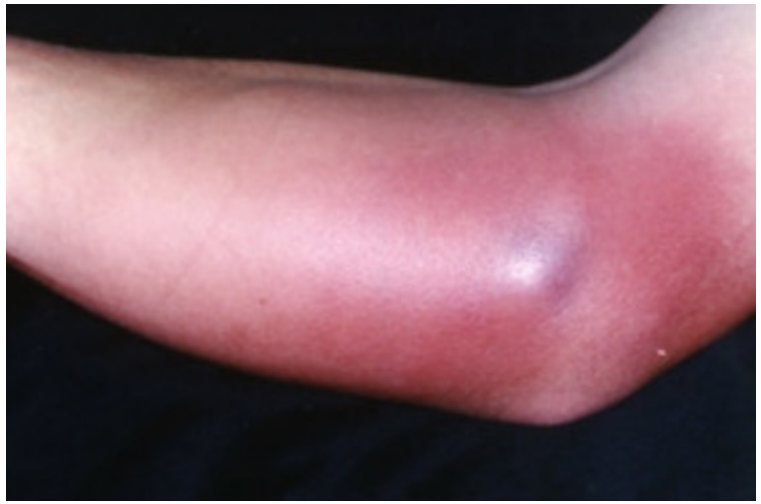
Outline

- How do you choose the correct antimicrobial for your patient?
- Antimicrobial susceptibility testing and interpretation
- Patient factors that influence antibiotic selection
- Antibiotic dosing and monitoring

Initial questions

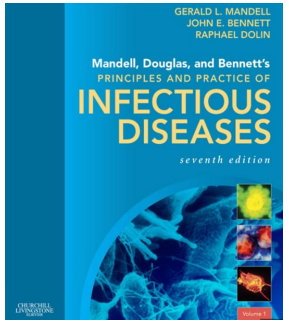
- Does the patient have an infection?
- Does the patient need urgent treatment?
- What is the likely source?
- What are the likely causative organisms?
- Does the patient need an antibiotic?

A previously healthy, non-immunocompromised patient develops cellulitis of the arm after a minor skin abrasion

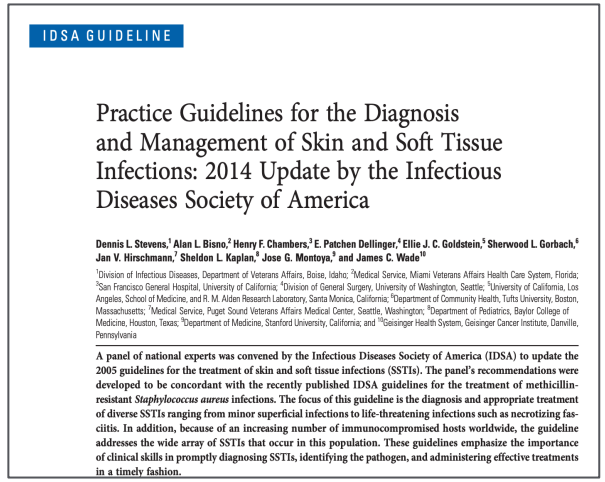


skin feels warm, red, swollen and painful.

Most common causes:
Streptococcus pyogenes
Other beta-hemolytic streptococci
Possibly Staphylococcus aureus



textbooks


IDSA GUIDELINE

Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America

Dennis L. Stevens,[1] Alan L. Bisno,[2] Henry F. Chambers,[3] E. Patchen Dellinger,[4] Ellie J. C. Goldstein,[5] Sherwood L. Gorbach,[6] Jan V. Hirschmann,[7] Sheldon L. Kaplan,[8] Jose G. Montoya,[9] and James C. Wade[10]

[1]Division of Infectious Diseases, Department of Veterans Affairs, Boise, Idaho; [2]Medical Service, Miami Veterans Affairs Health Care System, Florida; [3]San Francisco General Hospital, University of California; [4]Division of General Surgery, University of Washington, Seattle; [5]University of California, Los Angeles, School of Medicine, and R. M. Alden Research Laboratory, Santa Monica, California; [6]Department of Community Health, Tufts University, Boston, Massachusetts; [7]Medical Service, Puget Sound Veterans Affairs Medical Center, Seattle, Washington; [8]Department of Pediatrics, Baylor College of Medicine, Houston, Texas; [9]Department of Medicine, Stanford University, California; and [10]Geisinger Health System, Geisinger Cancer Institute, Danville, Pennsylvania

A panel of national experts was convened by the Infectious Diseases Society of America (IDSA) to update the 2005 guidelines for the treatment of skin and soft tissue infections (SSTIs). The panel's recommendations were developed to be concordant with the recently published IDSA guidelines for the treatment of methicillin-resistant *Staphylococcus aureus* infections. The focus of this guideline is the diagnosis and appropriate treatment of diverse SSTIs ranging from minor superficial infections to life-threatening infections such as necrotizing fasciitis. In addition, because of an increasing number of immunocompromised hosts worldwide, the guideline addresses the wide array of SSTIs that occur in this population. These guidelines emphasize the importance of clinical skills in promptly diagnosing SSTIs, identifying the pathogen, and administering effective treatments in a timely fashion.

Guidelines, literature reveiw

websites (e.g., Up to Date)

Don’t use ChatGPT (Artificial intelligence)

THE LANCET
Infectious Diseases

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ChatGPT and antimicrobial advice: the end of the consulting infection doctor?

Alex Howard • William Hope • Alessandro Gerada

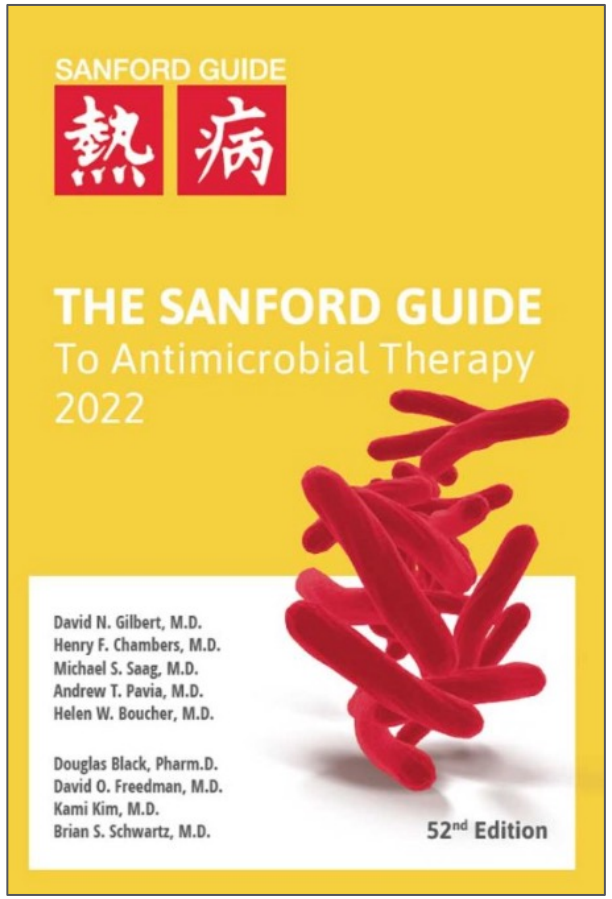
Published: February 20, 2023 • DOI: https://doi.org/10.1016/S1473-3099(23)00113-5

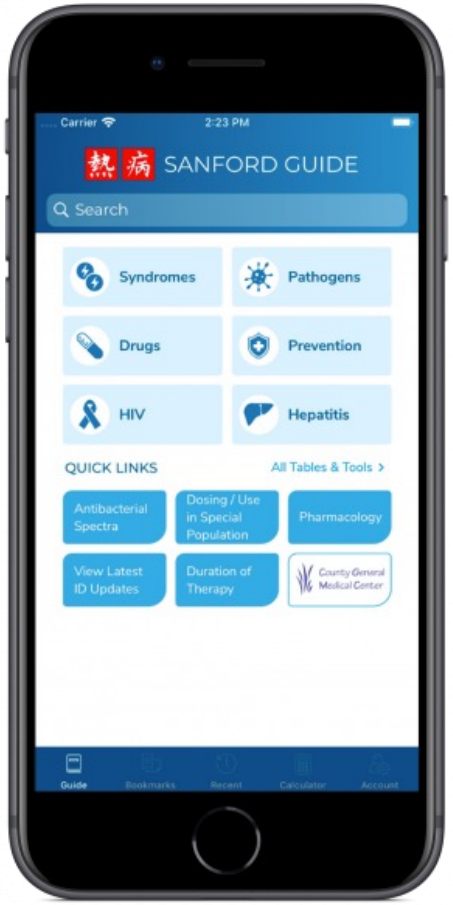
PlumX Metrics

Generative artificial intelligence (AI) models have proliferated in the past 2 years. ChatGPT—a

We conclude that the largest barriers to the implementation of ChatGPT in clinical practice are deficits in situational awareness, inference, and consistency. **These shortcomings could endanger patient safety.** ChatGPT appears to have access to sufficient training data, despite it not having access to specific medical databases. **Despite no specific clinical advice training, ChatGPT provides compelling responses to most prompts.**

Most popular antibiotic reference





Clinical Setting

- Treatment of uncomplicated cellulitis, erysipelas in extremities, non-diabetic; acute bacterial skin and skin structure infection (ABSSSI)
- Acute onset of rapidly spreading red edematous, tender plaque-like area of skin usually on the lower leg. Almost always unilateral. Often febrile.
- May be associated with lymphangitis or lymphadenitis.
- Portal of entry is frequently fungal infection between the toes (Tinea pedis).
- If facial skin is involved, see Facial erysipelas.
- Usually, can clinically distinguish between red indurated demarcated inflamed skin of erysipelas (*S. pyogenes*) from the abscess of *Staph. aureus*. Dual infection is rare. Bedside ultrasound may be helpful in detection of deep S.aureus abscess(es). I MRSA can mimic erysipelas; look for loculated purulence.
- Practice Guideline: Clin Infect Dis 59:147, 2014.
- In 216 patients with extremity non-purulent cellutlitis (erysipelas), the etiology was identified as a beta-hemolytic streptococcus (Group A, C, or G) in the vast majority: Open Forum Infect Dis 3:Nov 25, 2015, DOI: 10.1093/ofid/ofv181.
- **Beware of stasis dermatitis; often misdiagnosed as erysipelas**. See Comments.

Etiologies

- *Streptococcus pyogenes* (Groups A, B, C, G)
- *Staphylococcus aureus* (rare)

Primary Regimens

- Elevate the involved leg
- Inpatient parenteral therapy:
  - Penicillin G 1 to 2 million units IV q6h
  - If history of pencillin skin rash and nothing to suggest IgE-mediated allergic reaction:
    - Cefazolin 1 gm IV q8h or Ceftriaxone 2 gm IV once daily
  - If history/evidence of past IgE-mediated allergic reaction (anaphylaxis), then may be forced to use:
    - Vancomycin 15-20 mg/kg IV q8-12h to achieve preferred target AUC_{24} 400-600 µg/mL x hr (see vancomycin AUC dosing calculator); alternative is trough of 15-20 µg/mL
    - Linezolid 600 mg IV/po bid
  - Treat IV until afebrile; then outpatient Penicillin V-K 500 mg po qid ac and hs for a total of 10 days of therapy.
- Outpatient therapy for less-ill patients:
  - Penicillin V-K 500 mg po qid or Amoxicillin 500 mg po q8h OR
  - If history of penicillin skin rash and nothing to suggest an IgE-mediated reaction (anaphylaxis, angioneurotic edema):
    - Cephalexin 500 mg po qid for 10 days
  - If documented past history of IgE-medicated allergic reaction to beta-lactam antibiotics:
    - Azithromycin 500 mg po x 1 dose then 250 mg po qd x 4 days OR
    - Linezolid 600 mg po bid x 10 days or Tedizolid 200 mg po once daily x 6 days OR
    - Delafloxacin 450 mg po every 12 hr x 5-14 days OR
    - Omadacycline
      - 200 mg IV (over 60 min) loading dose and then 100 mg (over 30 min) q24 h OR
      - 100 mg IV over 30 min BID on day one and then 100 mg iv over 30 min q24h OR
      - 450 mg PO q24h on days 1 and 2 and then 300 mg PO q24h
      - Do not use an older tetracycline for reason of resistance and/or clinical failures.
- If clinically unclear whether infection is due to *S. pyogenes* or *Staph. aureus*, get cultures and start empiric therapy: Amoxicillin or Penicillin V-K or Cephalexin for *S. pyogenes* and TMP/SMX for *Staph. aureus* (MRSA). See Comment re TMP-SMX.

Alternative Regimens

- Acute bacterial skin and skin structure infections, moderately ill in-patient or out-patient who refuses hospitalization or is unlikely to comply with a multidose oral regimen, there are two very long acting vancomycin like drugs:
  - Dalbavancin 1 gm IV x 1 then 0.5 gm IV one week later (both by 30 min infusion) or 1.5 gm IV x 1
  - Oritavancin 1200 mg IV over 3 hrs
- For suspected *Staph. aureus* (fluctuance or positive gram stain):
  - MSSA (outpatient): Dicloxacillin 500 mg po qid

Pneumonia, Hospital-Acquired

by Henry F. Chambers, M.D. last updated Jun 2, 2022 8:32 PM

Empiric therapy for hospital-acquired pneumonia (HAP)

Clinical Setting

- Empiric therapy for hospital-acquired pneumonia.
- Pneumonia with onset 48 hours after hospital admission.
- Recommendations based on 2016 IDSA treatment guidelines (Clin Infect Dis 63:e61, 2016).
- Often associated with patients on mechanical ventilation (see ventilator-associated pneumonia for specific treatment recommendations).

Etiologies

- Early-onset: <5 days in the hospital, no other risk factors for multidrug-resistant (MDR) organisms
  - *Strep. pneumoniae*
  - *Staph. aureus*
  - *H. influenzae*
  - Enteric gram-negative bacilli
- Late-onset: ≥5 days in the hospital, risk factors for MDR organisms present
  - *Staph. aureus* (often MRSA)
  - Gram-negative entericsm often MDR. The following (ESKAPE) pathogens were etiology in nearly 80% of patients: Curr Opin Pulm Med 20:252, 2014.
    - ***E****schericia coli*
    - ***S****erratia marcescens*
    - ***K****lebsiella pneumoniae*
    - ***A****cinetobacter baumannii*
    - ***P****seudomonas aeruginosa*
    - ***E****nterobacter sp.*
  - Possible role of viruses
    - In non-ventilated hospital acquired pneumonia, film array multiplex PCR detected respiratory virus (rhinovirus, influenza, parainfluenza most often) in 22.4 %. Unclear whe
    - In study of patients with ventilator-associated pneumonia, 22.5% had respiratory virus (RSV or parainfluenza) in the airway: Am J Respir Crit Care Med 2012;186:325.

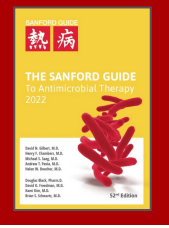
Primary Regimens

Initial questions, cont.

- Does the patient have an infection (differential diagnosis)?
- What is the likely source?
- What are the likely causative organisms?
- Does the patient need an antibiotic?
- Does the patient need urgent treatment?
- Is the antibiotic active against common microorganisms?
- Will the antibiotic achieve therapeutic concentrations at the site of infection?
- Does the patient need bactericidal antibiotics?*

* Concept of bactericidal versus bacteristatic has been questioned, but generally favors use of beta-lactam based regimens

Sanford guide spectrum tables



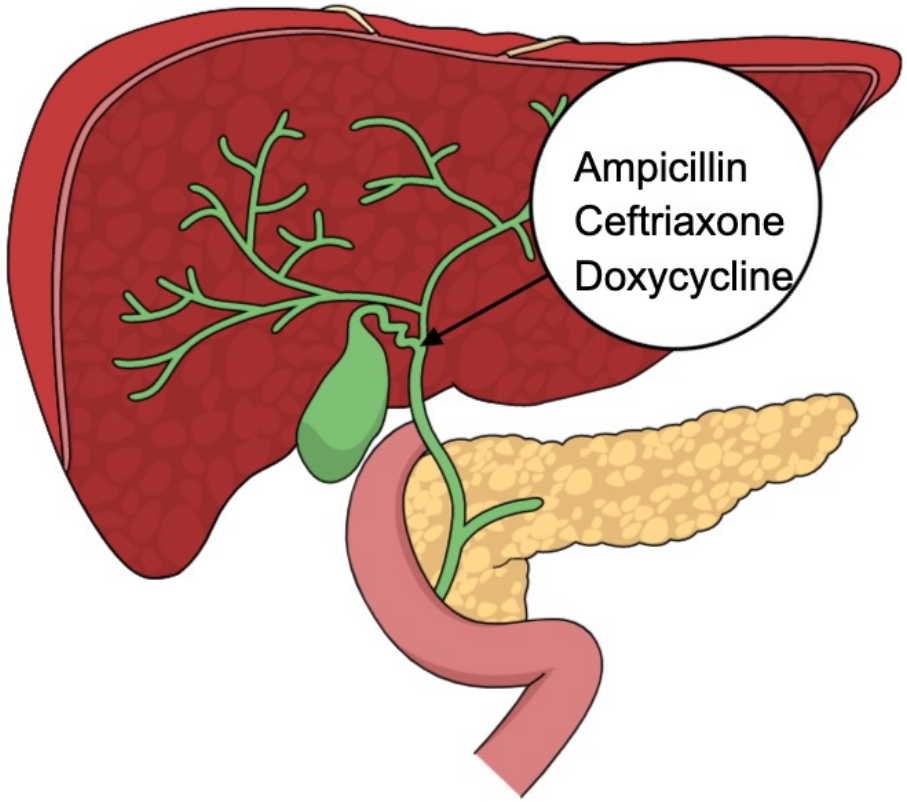
Antibacterial Agents: Spectra of Activity

by Editorial Board last updated Mar 26, 2021 1:50 PM © Antimicrobial Therapy, Inc.

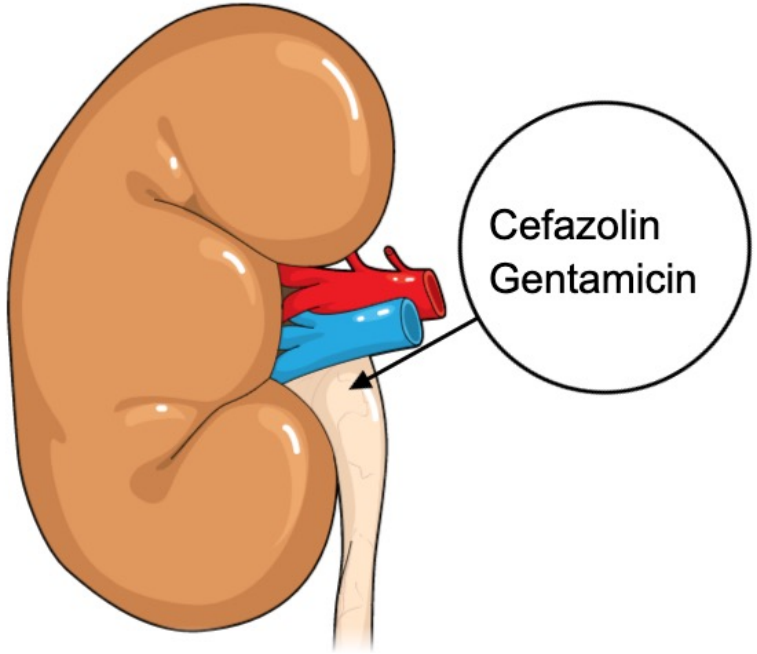
ADD ALL | ADD BUG/DRUG | PIVOT AXES | SEE LEGEND

	Penicillins												Carbapenems						M.	Fluoroquinolone									Parenteral Cephalosporins															Oral Cephalosporins										
	Penicillin G	Penicillin VK	Nafcillin	Oxacillin	Cloxacillin	Flucloxacillin	Dicloxacillin	Ampicillin	Amoxicillin	Amox-Clav	Amp-Sulb	Pip-Tazo	Doripenem	Ertapenem	Imp-cilastatin	Imp-cila-rele	Meropenem	Mero-Vabor	Aztreonam	Ciprofloxacin	Delafloxacin	Ofloxacin	Levofloxacin	Moxifloxacin	Norfloxacin	Prulifloxacin	Gemifloxacin	Gatifloxacin	Cefazolin	Cefotetan	Cefoxitin	Cefuroxime	Cefotaxime	Ceftizoxime	Cefoperazone	Ceftriaxone	Ceftazidime	Cefepime	Ceftaz-Avibac	Ceftaroline	Ceftobiprole	Ceftol-Tazo	Cefiderocol	Cefadroxil	Cephalexin	Cefaclor	Cefprozil	Cefurox-Axe	Cefixime	Ceftibuten	Cefpodoxime	Cefdinir	Cefditoren
S. aureus MRSA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	0	0	0	0	0	0	0	0	0	0	0
Staph coag-neg (MS)	±	±	++	++	++	++	++	±	±	+	+	+	+	+	+	+	+	+	0	0	+	0	+	+	0	0	+	+	++	+	+	+	+	+	+	+	0	+	0	+	+	0	0	+	+	+	+	+	0	0	+	+	+
Staph coag-neg (MR)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	0	±	±	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	0	0	0	0	0	0	0	0	0	0	0
S. epidermidis (MR)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	0	±	±	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	0	0	0	0	0	0	0	0	0	0	0
S. epidermidis (MS)	±	±	++	++	++	++	++	±	±	+	+	+	+	+	+	+	+	+	0	0	+	0	+	+	0	0	+	+	++	+	+	+	+	+	+	+	0	+	0	+	+	0	0	+	+	+	+	+	0	0	+	+	+
S. lugdunensis	±	±	++	++	++	++	++	±	±	+	+	+	+	+	+	+	+	+	0	0	+	+	+	+	0	0	+	+	++	+	+	+	+	+	+	+	0	+	0	+	+	0	0	+	+	+	+	+	0	0	+	+	+
S. saprophyticus	±	±	+	+	+	+	+	±	±	++	+	+	+	+	+	+	+	+	0	+	+	+	+	+	0	+	+	+	++	+	+	+	+	+	+	+	0	+	0	+	+	0	0	++	++	++	+	+	0	0	+	+	+
Strep. anginosus gp	++	++	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	±	+	±	±	±	0	±	±	±	+	+	+	+	+	+	+	+	±	+	±	+	+	+	0	+	+	+	+	+	+	+	+	+	+
Strep. pyogenes gp (A)	++	++	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	±	+	±	±	±	0	±	±	±	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+
Strep. agalactiae gp (B)	++	++	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	±	+	±	±	±	0	±	±	±	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+
Strep. gp C,F,G	++	++	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	±	+	±	±	±	0	±	±	±	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+
Strep. pneumoniae	++	++	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	±	+	±	+	+	0	±	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+
Viridans Strep.	±	±	±	±	±	±	±	±	±	±	±	±	+	+	+	+	+	+	0	0	+	0	+	+	0	0	+	+	+	+	+	+	++	+	+	++	±	+	±	+	+	+	0	+	+	+	0	+	+	0	+	+	+
Aerobic, gram positive bacilli																																																					

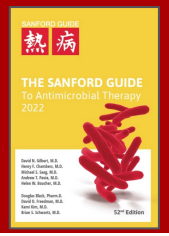
Where are antibiotic concentrated or excreted?



Cholangitis



Urinary tract infections



Sanford Guide

Example pharmacology summaries

Gentamicin

Dosing Data	
Pharmaceutical Preparations:	Injection, 0.1% cream, 0.1% ointment, 0.3% ointment, 0.3% eye drops
Pharmacologic Parameters	
PK/PD Index:	24-hr AUC/MIC
Peak Serum Conc (µg/mL)[2]:	4-6 (1.7 mg/kg IV, SD)
Peak Urine Conc (µg/mL):	No data
Protein Binding (%):	0-10
Volume of Distribution (Vd)[3]	0.26 L/kg
Avg Serum T½ (hr)[4]:	2-3
Elimination:	Renal
Bile Penetration (%)[5]	10-60
CSF/blood (%)[6]	0-30
Therapeutic Levels in CSF[7]	No
AUC (µg*hr/mL)[8]	70-100 (7 mg/kg, 0-inf)

2: SD = after a single dose, SS = at steady state

3: V/F = Vd/oral bioavailability; Vss = Vd at steady state; Vss/F = Vd at steady state/oral bioavailability

4: Assumes CrCl >80 mL/min

5: (Peak concentration in bile/peak concentration in serum) x 100. If blank, no data.

6: CSF concentrations with inflammation.

7: Judgment based on drug dose and organism susceptibility. CSF concentration ideally ≥10x MIC.

Ceftriaxone

Dosing Data	
Pharmaceutical Preparations:	Injection
Pharmacologic Parameters	
PK/PD Index:	T>MIC
Peak Serum Conc (µg/mL)[2]:	150 (1 gm IV, SD)
Peak Urine Conc (µg/mL):	No data
Protein Binding (%):	85-95
Volume of Distribution (Vd)[3]	5.8-13.5 L
Avg Serum T½ (hr)[4]:	8
Elimination:	Renal, biliary
Bile Penetration (%)[5]	200-500
CSF/blood (%)[6]	8-16
Therapeutic Levels in CSF[7]	Yes
AUC (µg*hr/mL)[8]	1006 (1 gm IV, 0-inf)

2: SD = after a single dose, SS = at steady state

3: V/F = Vd/oral bioavailability; Vss = Vd at steady state; Vss/F = Vd at steady state/oral bioavailability

4: Assumes CrCl >80 mL/min

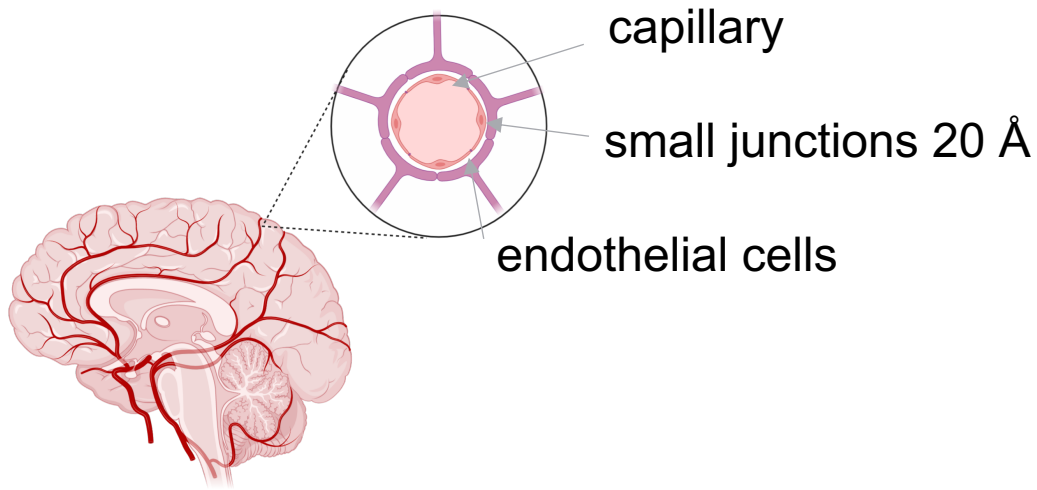
5: (Peak concentration in bile/peak concentration in serum) x 100. If blank, no data.

6: CSF concentrations with inflammation.

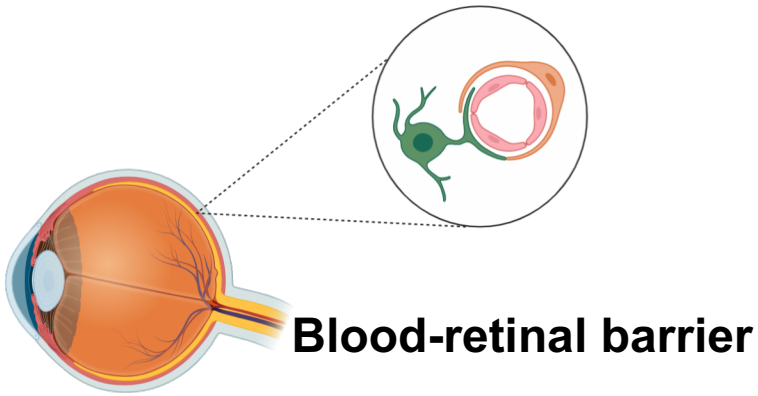
7: Judgment based on drug dose and organism susceptibility. CSF concentration ideally ≥10x MIC.

Antimicrobial penetration at the site of infection

Anatomically privileged sites

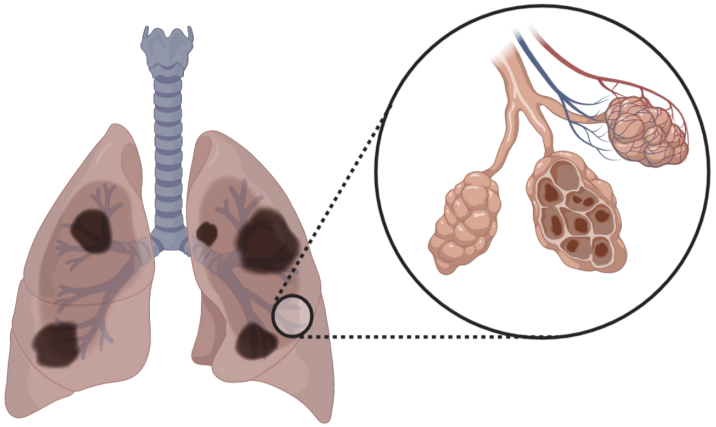


Blood-brain barrier



Blood-retinal barrier

Inflammation, abscess, necrosis



Antibiotic penetration influenced by:

- Serum drug concentrations
- Physiochemical properties of drugs
- Alterations in anatomic permeability (e.g., inflammation)
- Physiological barriers (e.g., blood-eye, blood brain barrier)
- Drug inactivation due to local pH, anaerobic conditions or enzyme activity

Daptomycin activity in community-acquired pneumonia

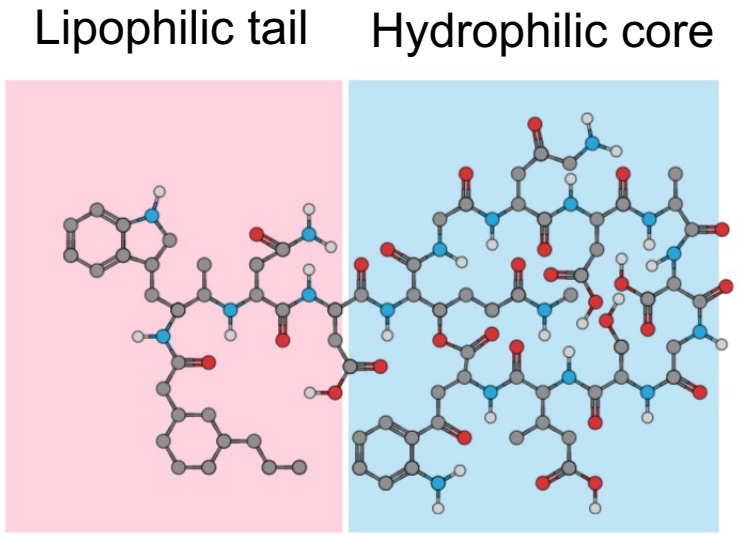
Table 4. Clinical cure rates by pooled study population.

Population	Daptomycin arm		Ceftriaxone arm		95% CI[a]
	No. of patients cured/total no. of patients	Cure rate, %	No. of patients cured/total no. of patients	Cure rate, %	
Intent-to-treat	293/413	70.9	326/421	77.4	−12.4% to −0.6%
Modified intent-to-treat	98/132	74.2	92/116	79.3	−15.6% to 5.4%
Clinically evaluable	293/369	79.4	326/371	87.9	−13.8% to −3.2%

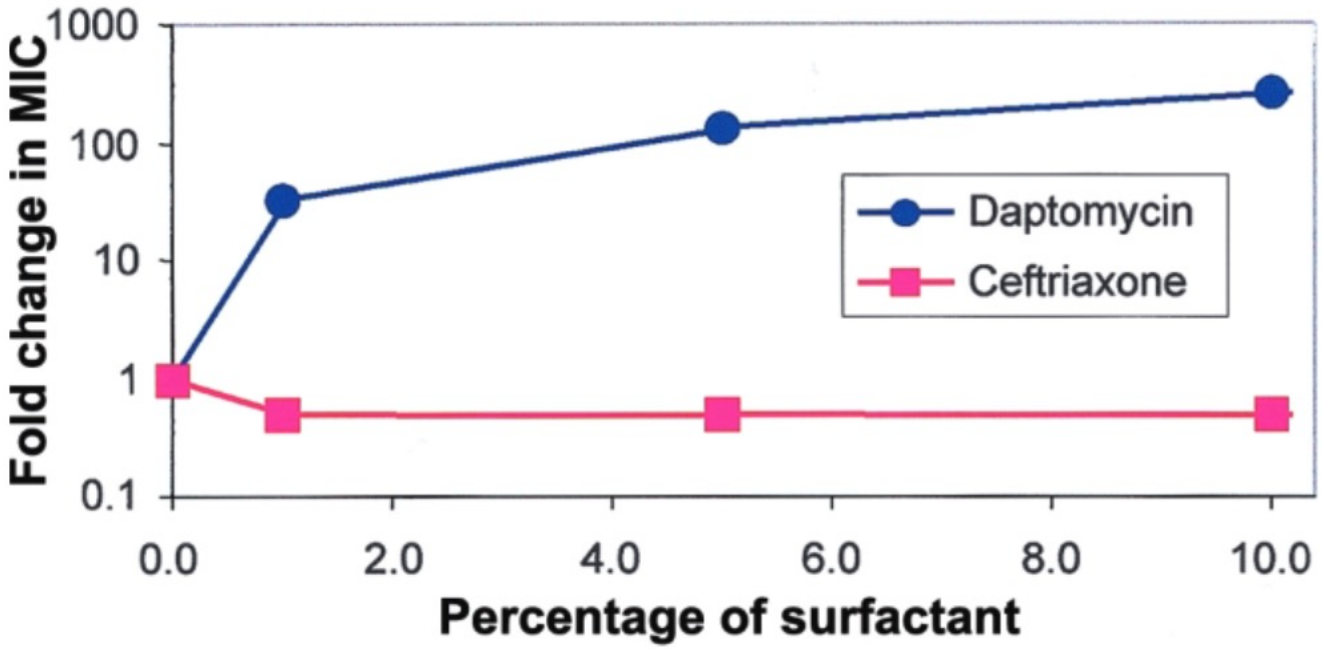
[a] For the difference in cure rates.

Pertel PE et al. Clin Infect Dis 2008; 46:1142–1151.

Daptomycin is inhibited by pulmonary surfactant

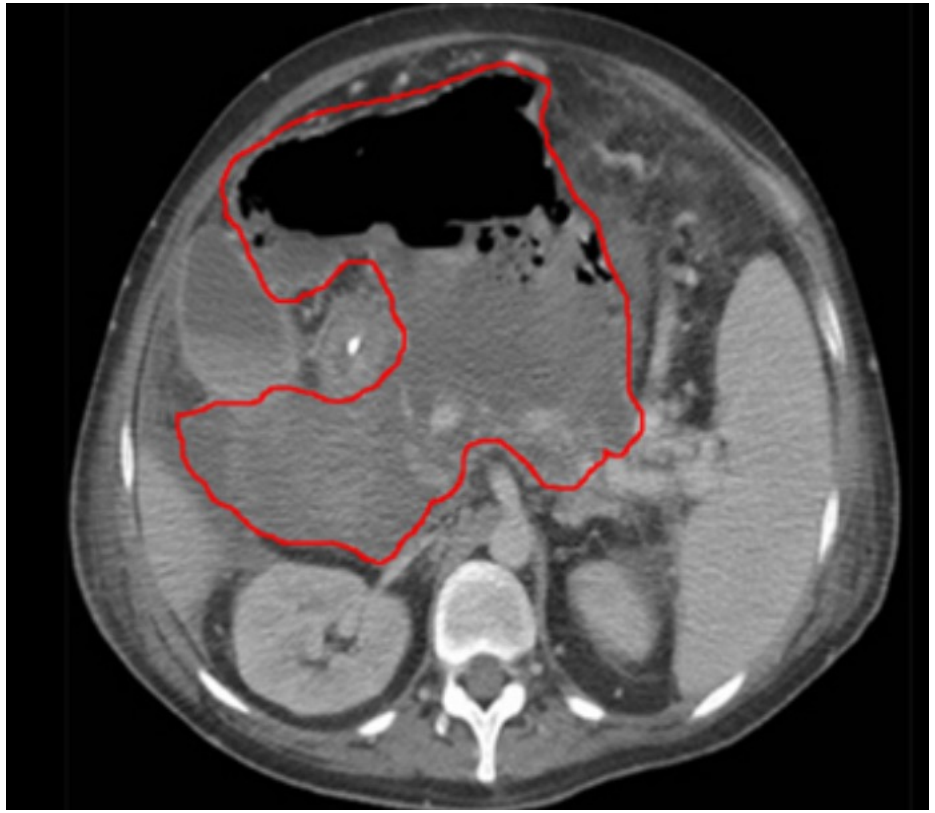


Daptomycin molecule



Silverman JA et al. J Infect Dis 2005; 191:2149–2152.

Abscess



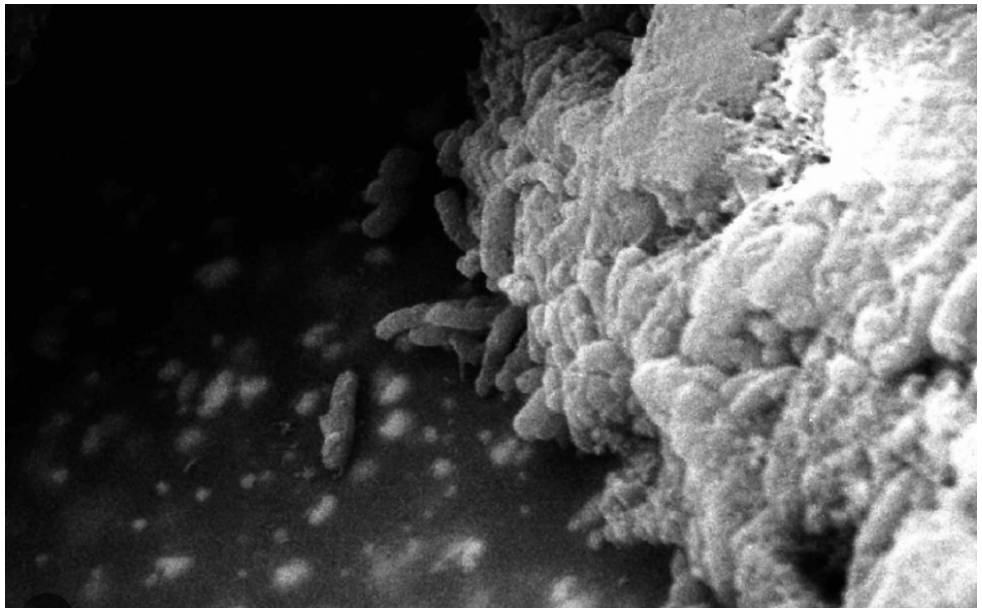
Post-operative intraabdominal abscess
Image: *BMJ*

- **Aminoglycosides**
  - Bind and are inactivated by purulent material
  - Decrease aminoglycoside uptake into facultative aerobic bacteria
  - Decreased at low pH
- **Penicillins and tetracyclines are bound by hemoglobin, less effective with hematoma formation**
- **Emphasizes importance of source control** (abscess drainage, removal of prosthetic materia)

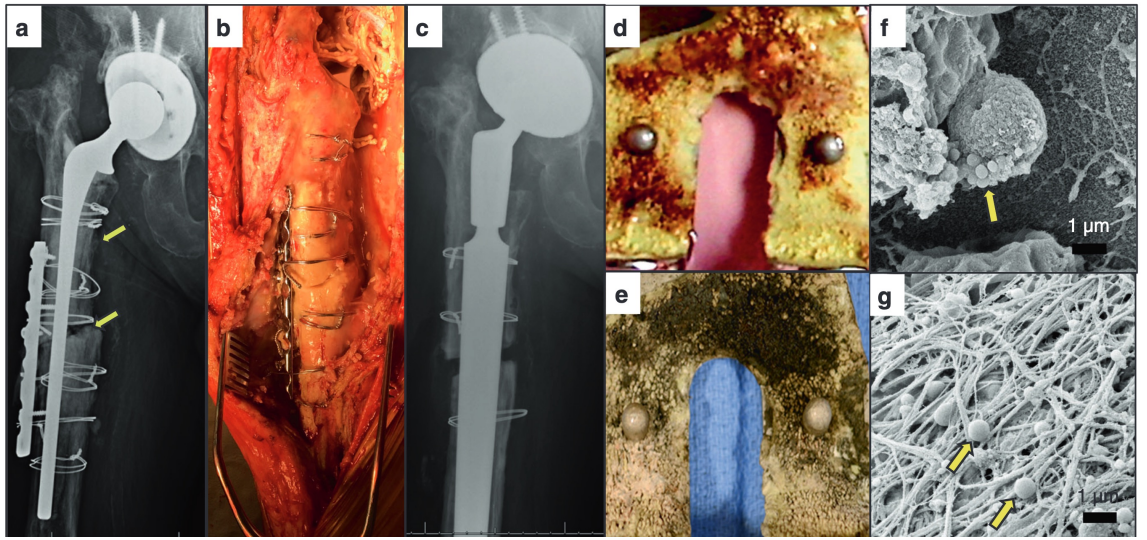
Foreign bodies and biofilm

Common source control problems

SEM of urinary catheters



Prosthetic joints and implant infections



Masters EA. Bone Res 2019; 7:20.

Subpopulation of bacteria in a biofilm are in a dormant metabolic state and not inhibited by antimicrobials:
can disperse and cause recurrent infections/bacteremia

Initial questions

- Does the patient have an infection (differential diagnosis)?
- What is the likely source?
- What are the likely causative organisms?
- Does the patient need an antibiotic?
- Does the patient need urgent treatment?
- Is the antibiotic active against common microorganisms
- Will the antibiotic achieve therapeutic concentrations at the site of infection?
- Which route of administration- IV or oral?

Oral antibiotics, coverage and bioavailability
(% oral bioavailability)

Staphylococcus (MRSA)	**Enterococcus**	**Streptococcus**	**Enterobacterales**	**Pseudomonas**
Linezolid (100%) TMP/SMX (90-100%) Doxycycline (95%) Delafloxacin (90%)	Linezolid (100%) Ampicillin (50%) Nitrofurantoin [urine] (80%) Amox/Clav (85%)	**GAS/GBS** Penicillin VK (50%) Amoxicillin (85%) Cephalexin (90%) Levofloxacin (99%) Clindamycin (90%) Linezolid (100%)	Ciprofloxacin (70%) Levofloxacin (99%) Moxifloxacin (90%) Amox/Clax (85%) Cefixime (40-50%) Cefuroxime (70%) Cephalexin (90%) TMP/SMX (90-100%)	Ciprofloxacin (70%) Levofloxacin (99%) Delafloxacin (60%)
Staphylococcus (MSSA) Cephalexin (90%) Dicloxacillin (50-75%)		**S. pneumoniae** Amoxicillin (85%) Doxycycline (95%) Azithromycin (30-50%) Levofloxacin (99%)		

Source: Sanford's Guide; GAS- group A. streptococcus; GAB-Group B streptococcus; MRSA- methicillin-resistant; MSSA- Methicillin-sensitive *S. aureus*
Some Antibiotic bioavailably is affected by food, gastric acidity and chelating agents (drug interactions)

When is switch to oral therapy from IV safe?

If YES to all, consider oral therapy…	If YES to any, continue IV…
Is patient able to swallow and tolerate oral fluids?	Does the patient have problems swallowing
Is patient's fever < 38°C for 24-48 hours	Does the patient have continuing sepsis?
Respiratory rate < 20 bpm	Does the patient have an infection that indicates need for IV antibiotics? -Meningitis -Infective endocarditis* -Encephalitis -Osteomyelitis* -Febrile neutropenia
Heart rate < 100 bpm 12 hours	
Is patients C-reactive protein (CRP) decreasing	
Are oral formulations available?	

*Oral regimens increasingly studied for these indications

Other patient specific factors to consider…

- History of previous adverse reactions or allergies to antimicrobial agents…*we will discuss in detail in future lecture*
- Patient age
- Renal and hepatic function …*will discuss in part 2.*
- Genetic or metabolic abnormalities (e.g., G6PD deficiency)
- Metabolic disorders (diabetes) – sulfonamides, fluoroquinolones, dextrose in IV fluids
- Drug interactions

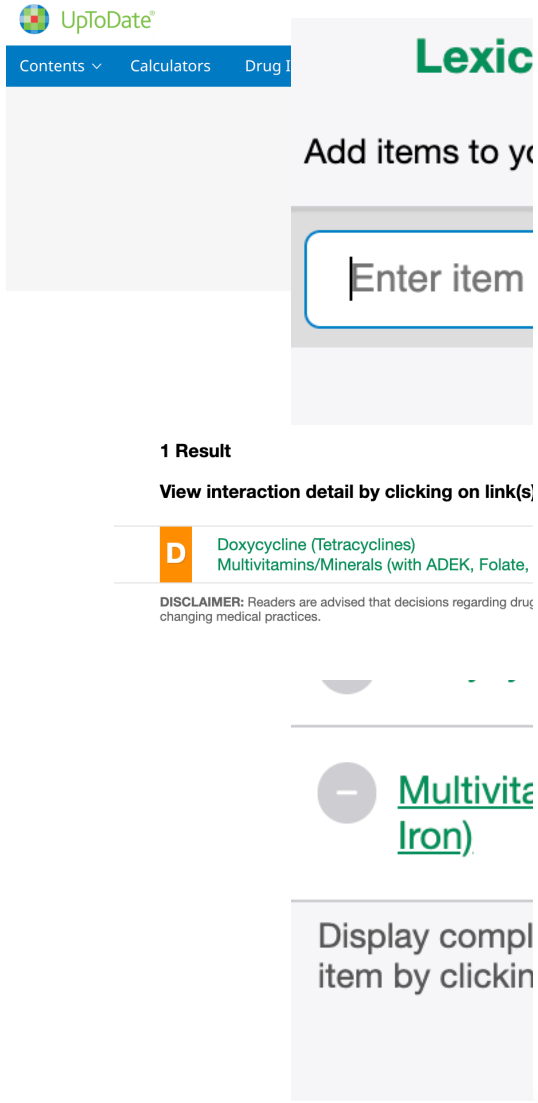
Sanford's drug interactions

Doxycycline

Interaction with Other Drugs

Al, Bi, Fe, Mg (e.g. antacids)	
Effect:	↓doxycycline absorption
Suggested Management:	Avoid co-administration
Barbiturates	
Effect:	↓doxycycline
Suggested Management:	Avoid co-administration
Carbamazepine	
Effect:	↓doxycycline
Suggested Management:	Avoid co-administration
Digoxin	
Effect:	↑digoxin
Suggested Management:	Monitor, adjust dosage
Phenytoin	
Effect:	↓doxycycline
Suggested Management:	Avoid co-administration
Rifampin	
Effect:	↓doxycycline
Suggested Management:	Adjust dosage or avoid
Sucralfate	
Effect:	↓doxycycline absorption
Suggested Management:	Avoid co-administration
Warfarin	
Effect:	↑INR
Suggested Management:	Monitor INR, adjust dosage

Lexicomp- Up to Date Drug Interactions



Title Tetracyclines / Multivitamins/Minerals (with ADEK, Folate, Iron)

Print

Dependencies

- **Route**: This interaction only applies to use of oral tetracyclines.

Risk Rating D: Consider therapy modification

Summary Multivitamins/Minerals (with ADEK, Folate, Iron) may decrease the serum concentration of Tetracyclines. **Severity** Major **Reliability Rating** Fair

Patient Management In general, the coadministration of oral polyvalent cations (ie, calcium, magnesium, zinc, iron) and oral tetracycline derivatives should be avoided. Interactions may be minimized by administering the polyvalent cation-containing multivitamin at least 2 hours before or 4 hours after the dose of the oral tetracycline derivative. Even with dose separation, therapy may still be compromised. Monitor for decreased therapeutic effect of oral tetracycline derivatives.

Tetracyclines Interacting Members Demeclocycline, Doxycycline, Lymecycline, Minocycline (Systemic), Omadacycline, Oxytetracycline, Sarecycline, Tetracycline (Systemic)
Exceptions (agents listed are discussed in separate interaction monograph[s] or are non-interacting) Eravacycline, Tigecycline

Discussion Several studies have shown that the absorption/bioavailability of tetracycline, minocycline, doxycycline, and oxytetracycline were significantly reduced by the concurrent use of the polyvalent cations calcium, magnesium, or iron.[1,2,3,4,5,6,7] Similarly, serum concentrations and AUC of the tetracyclines have been shown to be reduced by as much as 40-50% with concurrent ingestion of magnesium and zinc salts.[8,9,10,11]

This interaction is likely the result of formation of a non-absorbable cation-tetracycline complex in the GI tract.[12] Separating the doses of the cation and the tetracycline by 2-4 hours appears to have a minimizing effect on the interaction.[3,4] However, even with the recommended dose separation, use of such a combination may still result in significant decreases in tetracycline derivative absorption.[4]

Footnotes

1. Tetracycline [prescribing information]. Sellersville, PA: Teva Pharmaceuticals USA; June 2009.

2. Minocin (minocycline) [prescribing information]. Cranford, NJ: Triax Pharmaceuticals, LLC; August 2010.

3. Vibramycin (doxycycline) [prescribing information]. New York, NY: Pfizer Inc; April 2007.

4. Jung H, Peregrina AA, Rodriguez JM, et al. The influence of coffee with milk and tea with milk on the bioavailability of tetracycline. *Biopharm Drug Dispos*. 1997;18(5):459-463. [PubMed 9210983]

5. Garty M, Hurwitz A. Effect of cimetidine and antacids on gastrointestinal absorption of tetracycline. *Clin Pharmacol Ther*. 1980;28(2):203-207. [PubMed 7398187]

6. Leyden JJ. Absorption of minocycline hydrochloride and tetracycline hydrochloride. Effects of food, milk and iron. *J Am Acad Dermatol*. 1985;12:308-312. [PubMed 3838321]

7. Neuvonen PJ, Gothoni G, Hackman R, et al. Interference of iron with the absorption of tetracyclines in man. *Br Med J*. 1970;4:532. [PubMed 5483323]

8. Healy DP, Dansereau RJ, Dunn AB, et al. Reduced tetracycline bioavailability caused by magnesium aluminum silicate in liquid formulations of bismuth subsalicylate. *Ann Pharmacother*. 1997;31(12):1460-1464. [PubMed 9416381]

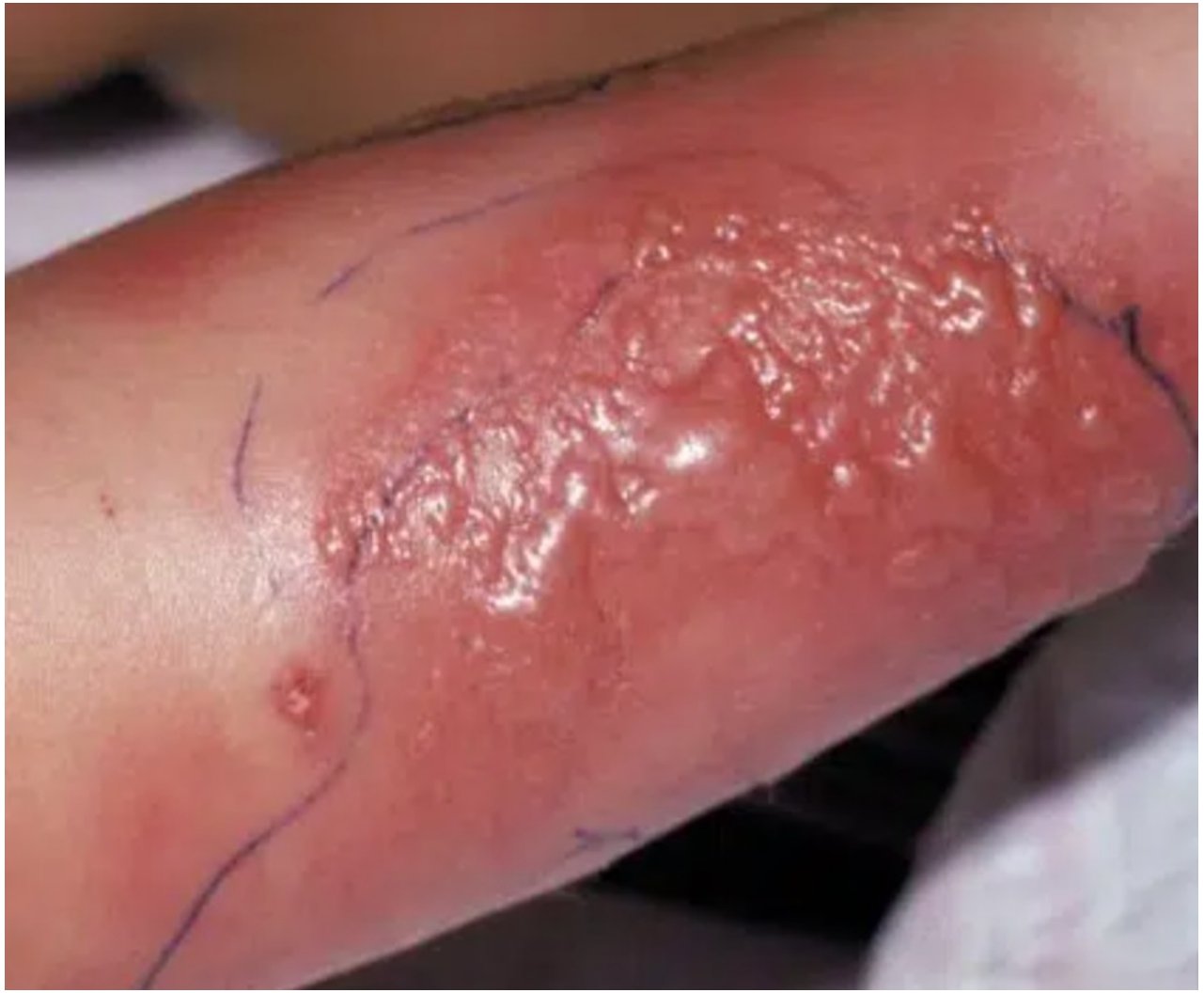
9. Penttila O, Hurme H, Neuvonen PJ. Effect of zinc sulphate on the absorption of tetracycline and doxycycline in man. *Eur J Clin Pharmacol*. 1975;9:131. [PubMed 786686]

10. Andersson KE, Bratt L, Dencker H, et al. Inhibition of tetracycline absorption by zinc. *Eur J Clin Pharmacol*. 1976;10:59.

Other common patient-specific factors, cont.

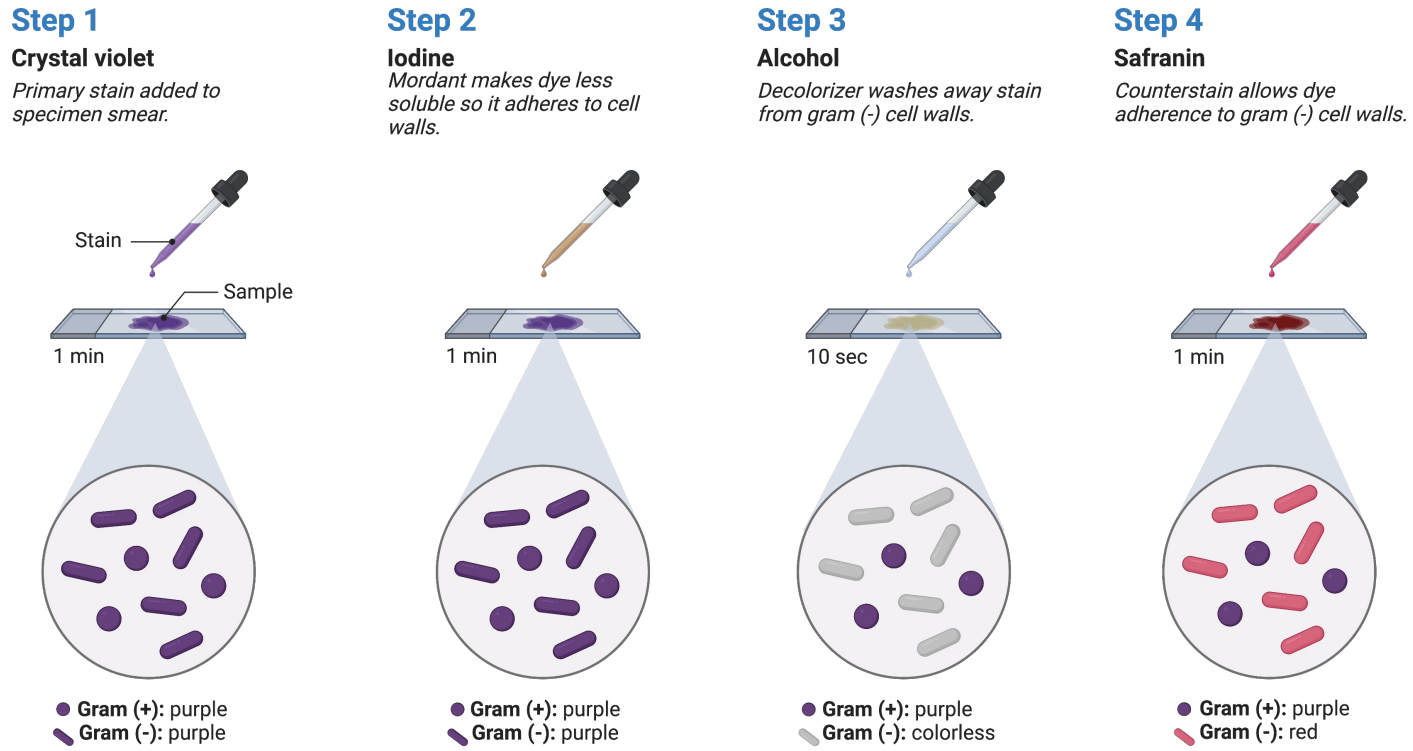
- **QTc interval prolongation (*Torsades des pointes*)**
  - **Macrolides, fluoroquinolones, azole antifungals, etc.**
- **Pregnancy**

A sample is sent for culture…



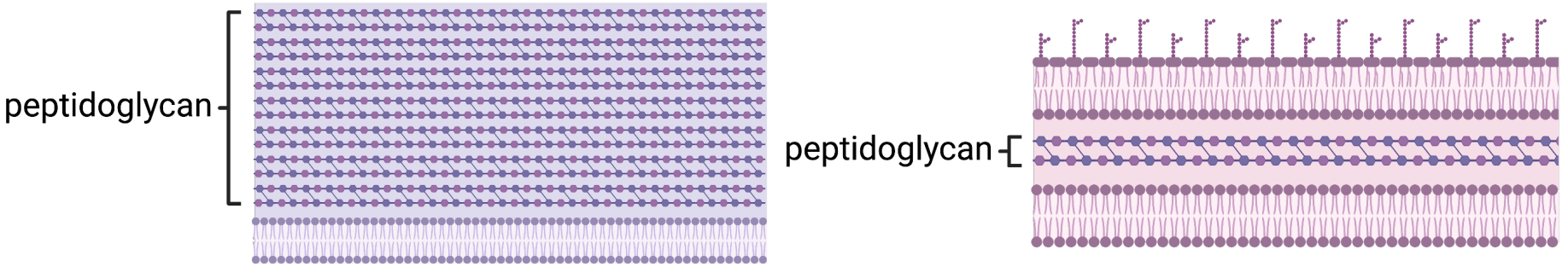
Gram stain

Most useful test for selecting antimicrobial spectrum



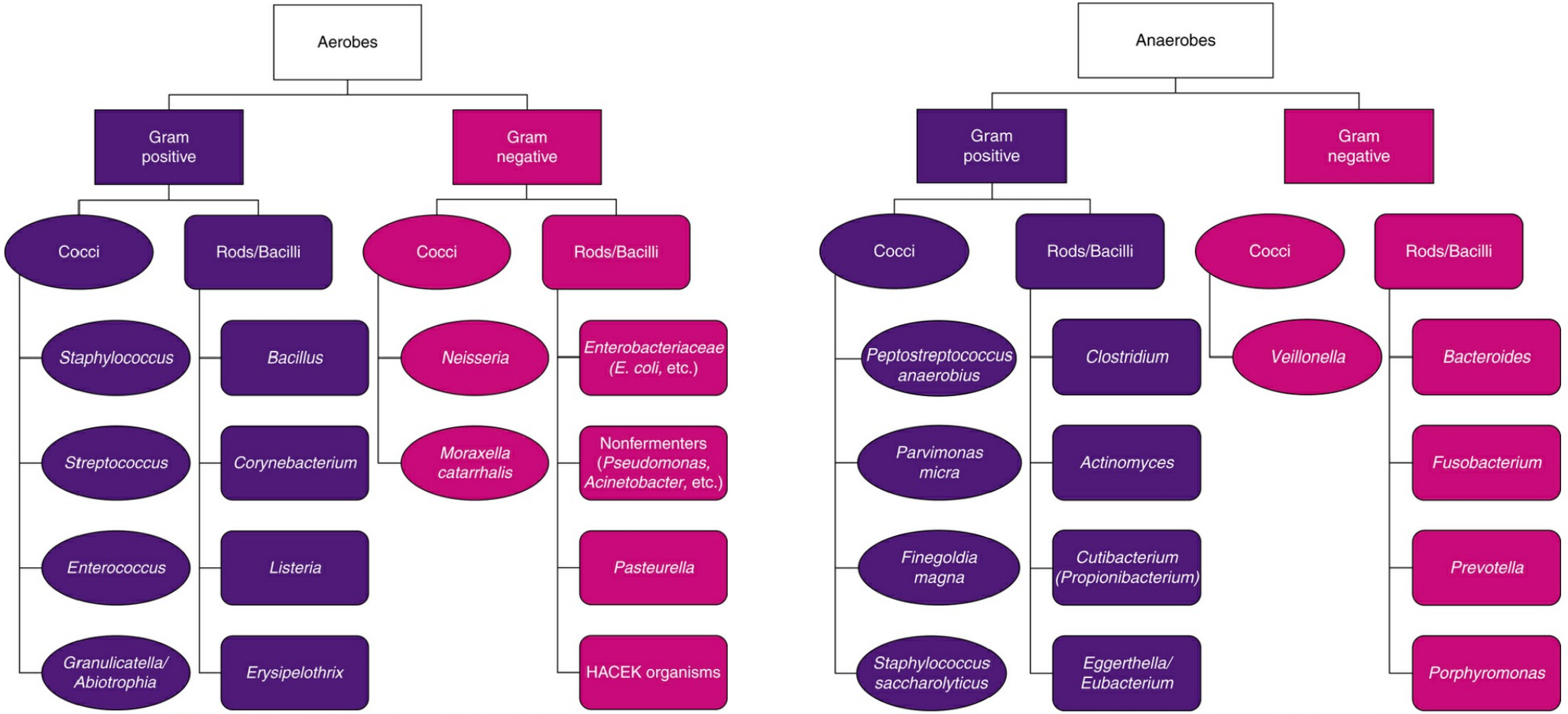
Gram positive

Gram negative



Gram stain + morphology

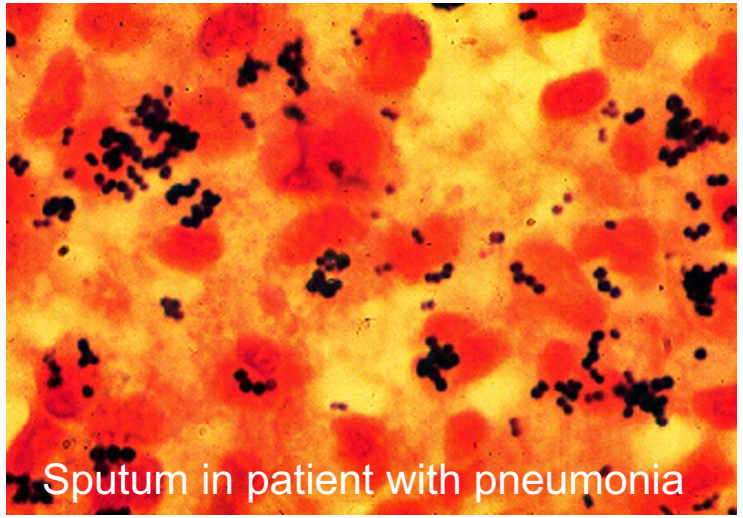
Typically performed for body fluids that are normally sterile

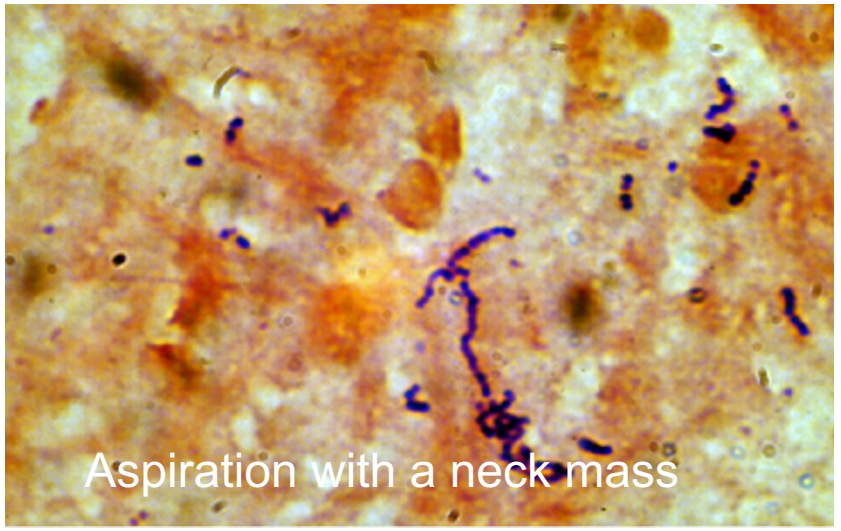


Figures: Spec A, Escota G, Chrisler and Davies, *Comprehensive Review of Infectious Diseases 2020*

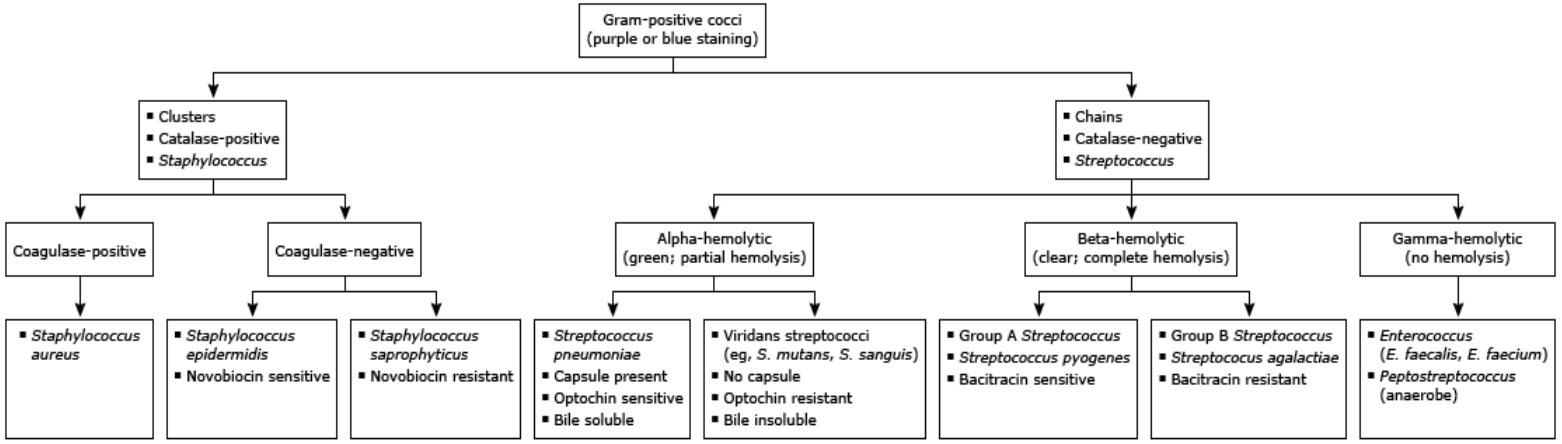
Not some organisms cannot be visualized by Gram stain because they lack cell wall (Myocoplasma spp) or cell wall does not retain stain (eg, Chlamydia spp)

Gram stain + morphology+ bacterial characteristics


Sputum in patient with pneumonia

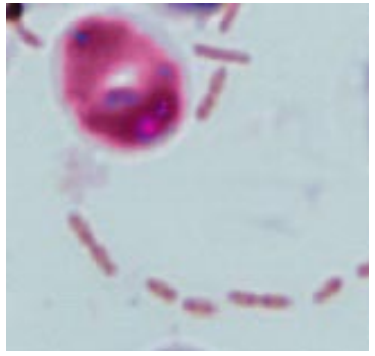

Aspiration with a neck mass

Classification of gram-positive cocci by laboratory features

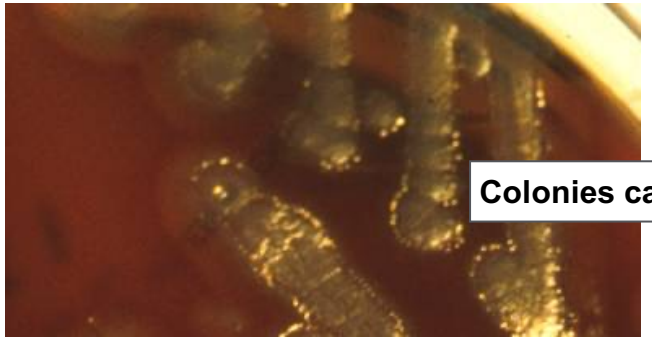


Biochemical methods
simple spot methods (e.g, catalase, oxidase, coagulase)

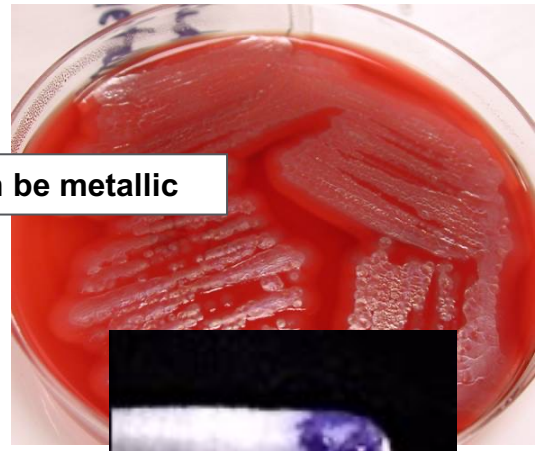
Pseudomonas aeruginosa



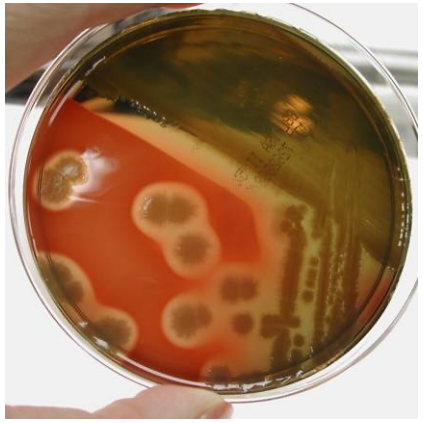
Gram – rods (In blood culture) longer & thinner than enteric rods

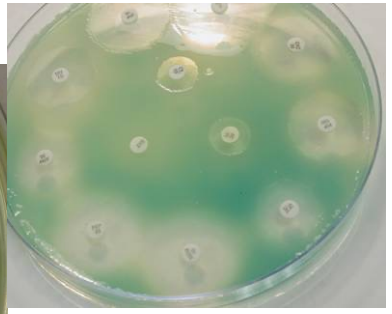


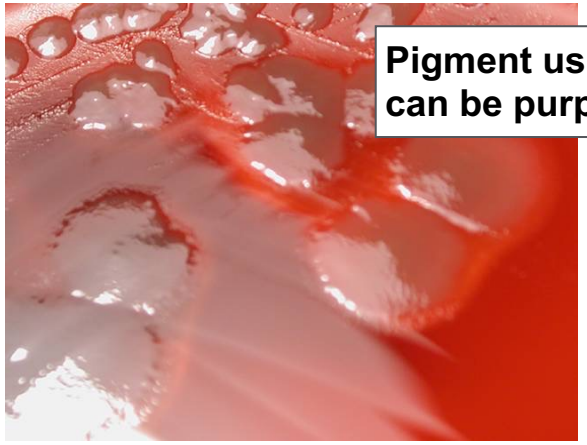
Colonies can be metallic



- Rough colonies on BAP
- Non-lactose fermenters on MacConkey
- Usually beta hemolytic
- Grape-like smell
- Oxidase positive





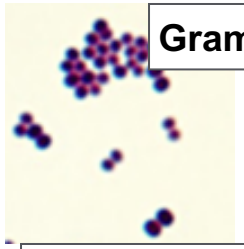


Pigment usually green but can be purple or blue

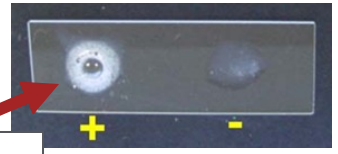
Slide: Ellen Jo Baron 2007

Biochemical methods

simple spot methods (e.g., catalase, oxidase, coagulase)

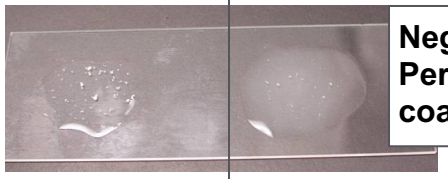


Gram + cocci clusters

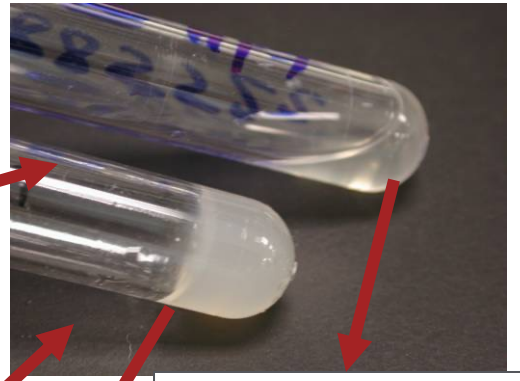


Catalase positive

Slide coagulase

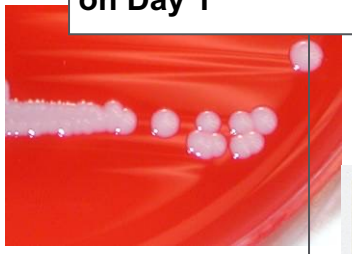


Negative
Perform tube coagulase test

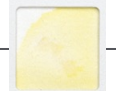


Positive
Typical hemolytic colony
Staphylococcus aureus

Positive but clumpy
Colony more white; non-hemolytic
on Day 1



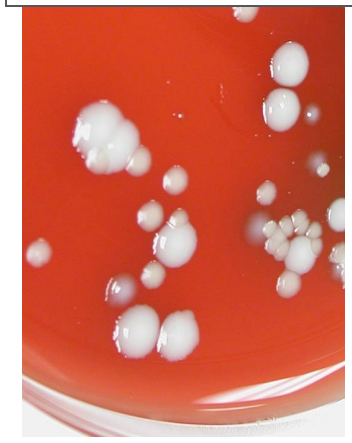
PYR negative
Perform tube coagulase test



PYR positive
Staphylococcus lugdunensis

If tube coagulase positive:
Staphylococcus aureus

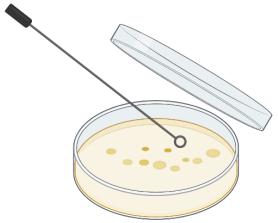
If PYR and coagulase negative:
Coagulase negative staphylococci



Staphylococci

Slide: Ellen Jo Baron 2007

Evolution of bacterial identification

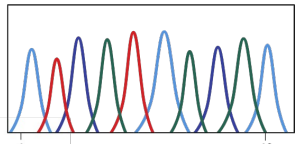


Automated phenotypic tests

Conventional phenotypic tests

Bacterial identification

16s rDNA sequencing



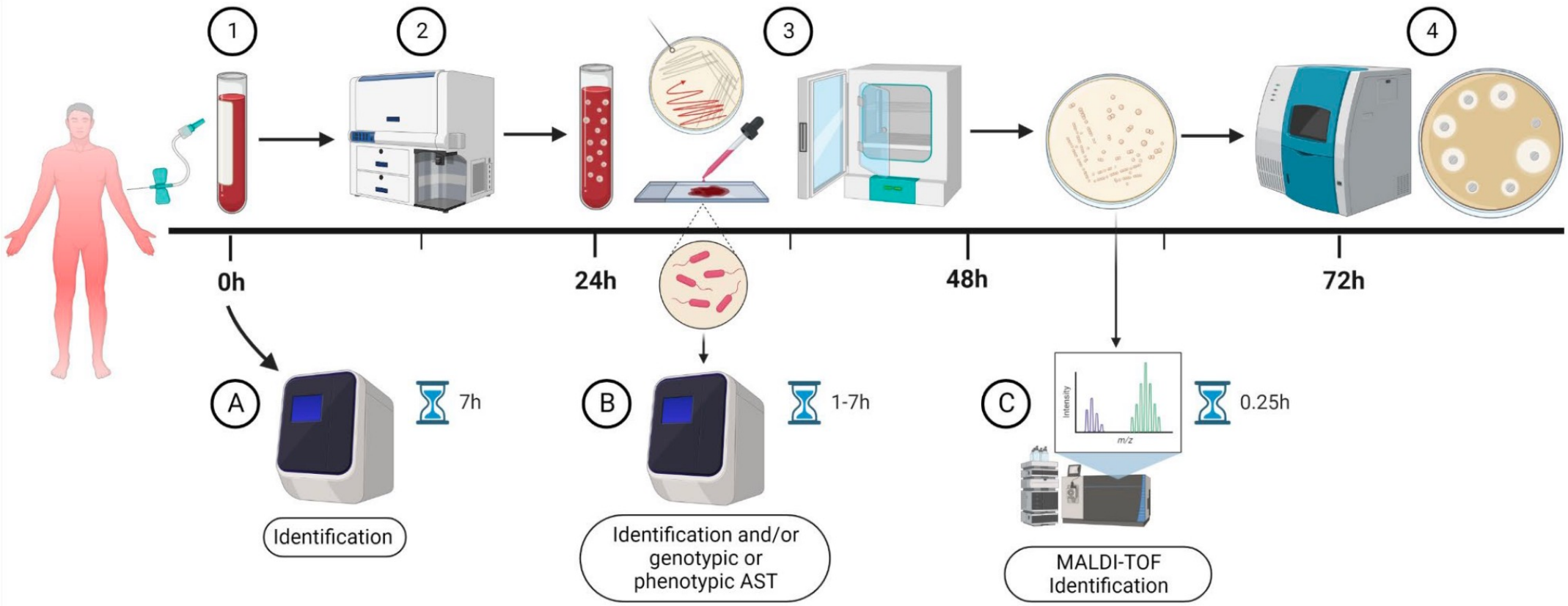
Molecular tests

RT-PCR

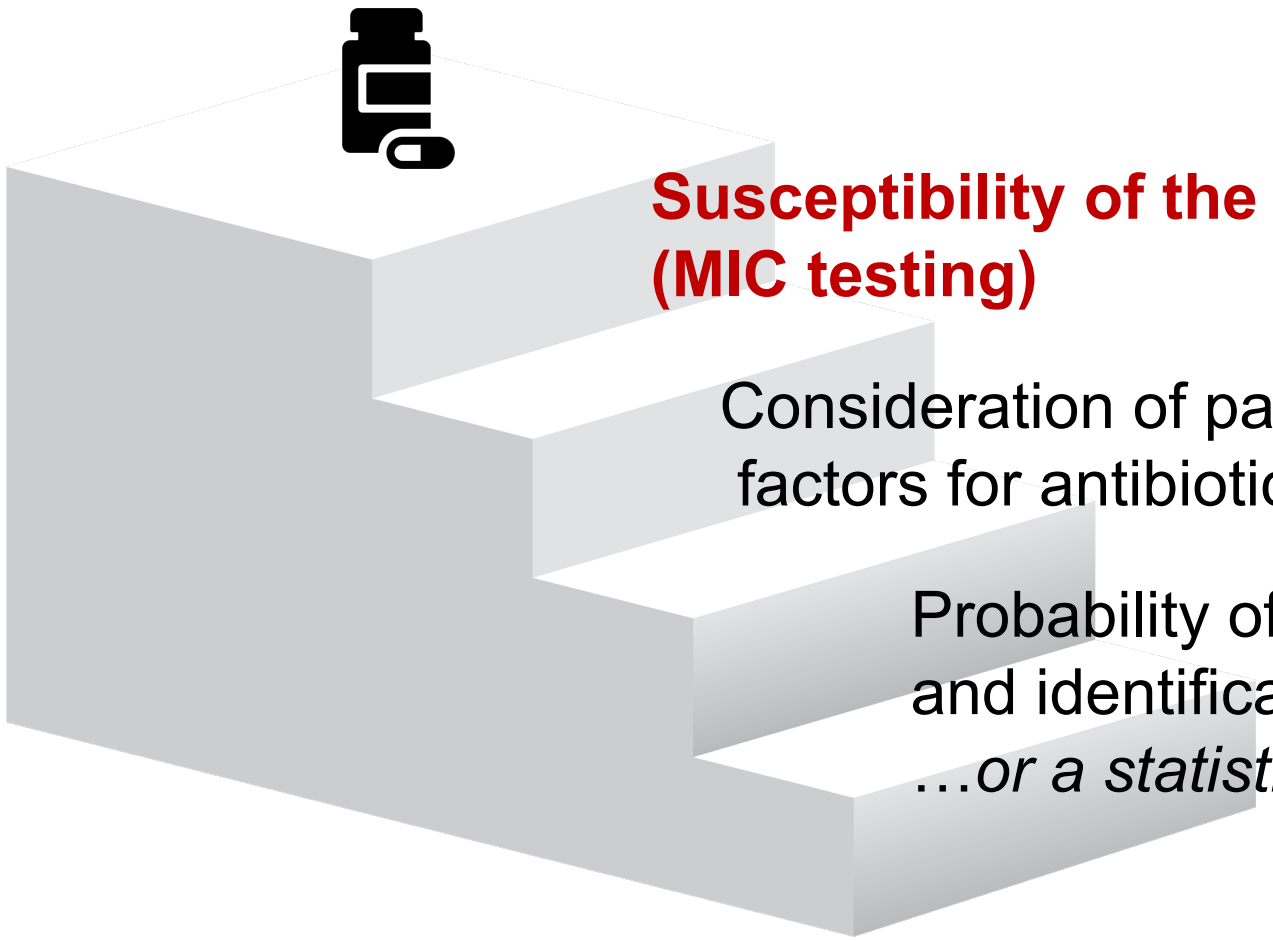
Matrix-Assisted Laser Desorption/ Ionization – Time of Flight (MALDI-TOF)

Older techniques such as antisera have been replaced by molecular techniques and proteomic methods (MALDI-TOF)

Timeline towards positive identification



Wenzler E et al. Pharmacotherapy 2023



Susceptibility of the infecting organism (MIC testing)

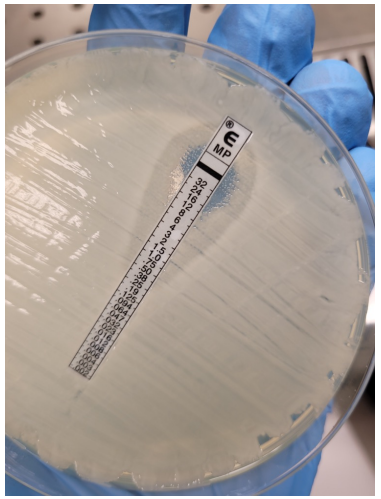
Consideration of patient-specific factors for antibiotic therapy

Probability of infection (differential dx) and identification of the infecting organism

…*or a statistically reasonable guess*

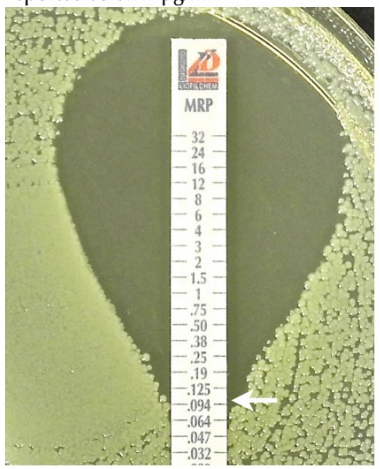
Mean inhibitory concentration (MIC)

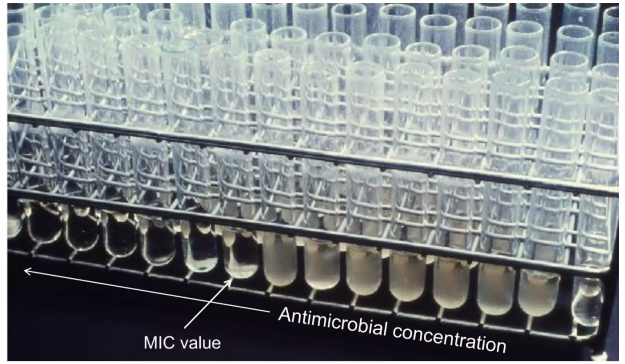
Disk difffusion (Kirby-Baur)



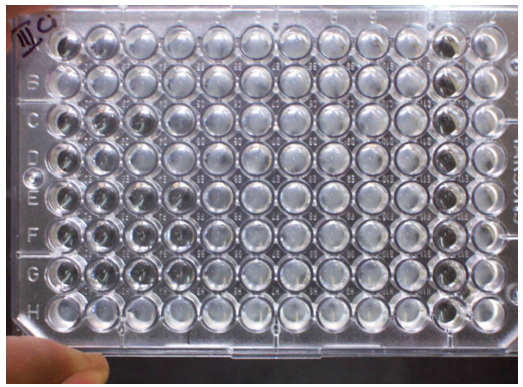
Gradient strips

Example 1:
E. cloacae, MRP MIC = 0.094 µg/mL,
reported as 0.12 µg/mL

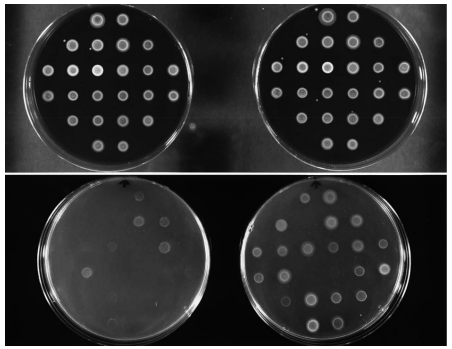




Macrodilution



Microdilution



Agar dilution (anaerobes)

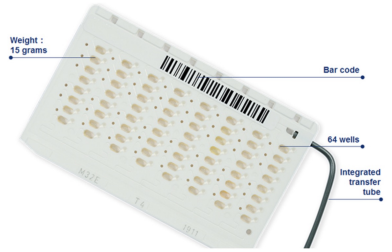
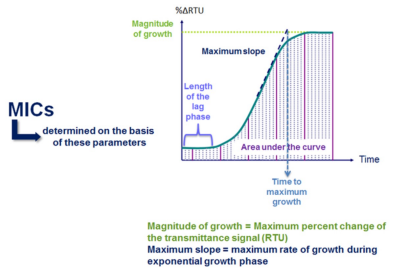
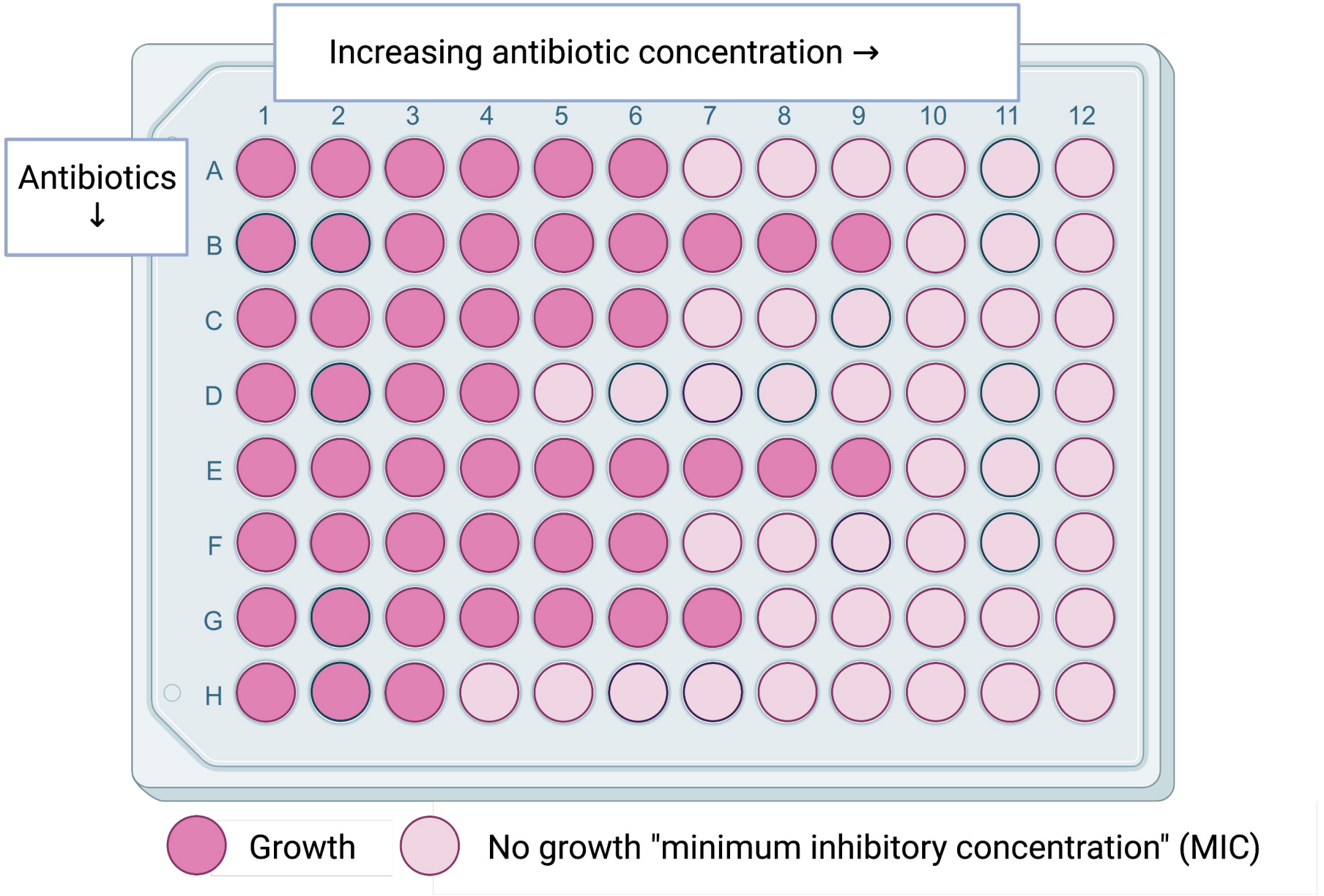


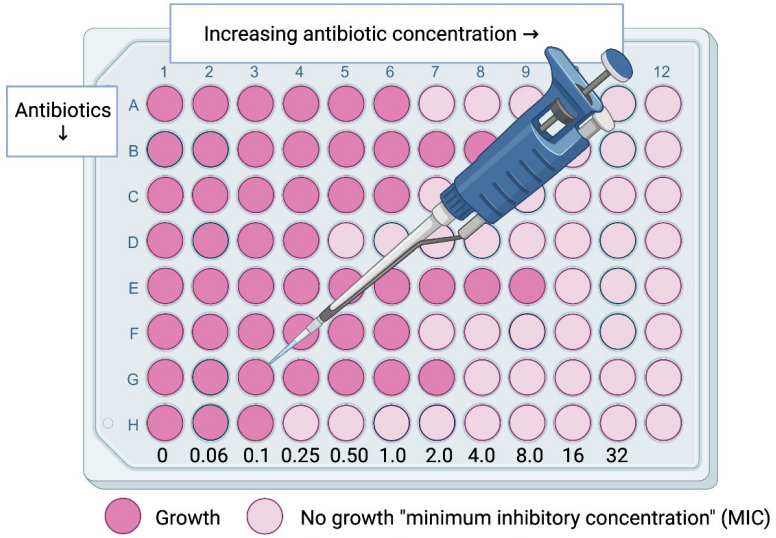
Figure 1: VITEK® 2 AST Card
Click to enlarge



Automated testing
(i.e. VITEK 2)

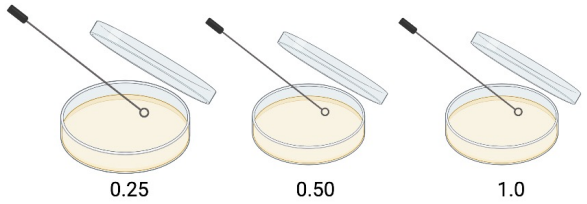
MIC


Increasing antibiotic concentration →
Antibiotics ↓
1 2 3 4 5 6 7 8 9 10 11 12
A
B
C
D
E
F
G
H
Growth
No growth "minimum inhibitory concentration" (MIC)

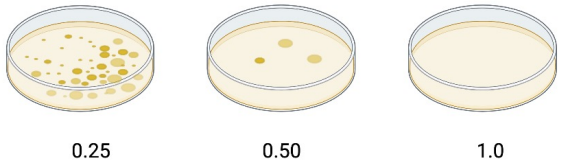


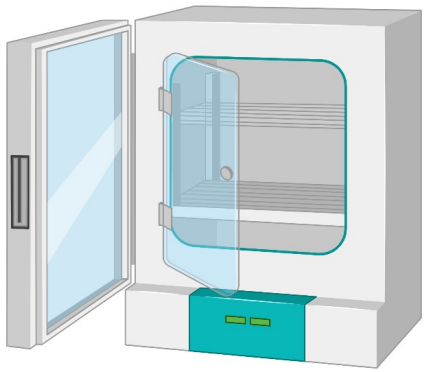
MIC 0.25 µg/mL

32-fold MBC > MIC = “Tolerance”



incubate for 24 hours





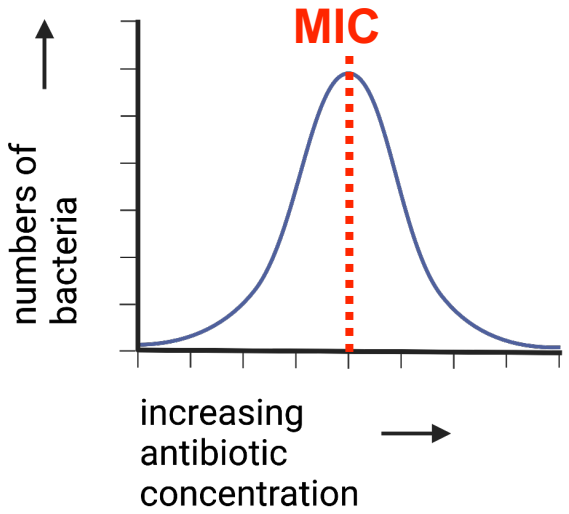
MBC 1 µg/mL

MBC: Indicative of 3-log orders of magnitude (99.9%) killing-“bactericidal”

Important things to remember about MICs

- **An estimation of antibiotic potency**
- **Does not reflect *in vivo* conditions**
  - Standardized inoculum $5x10^4$ for testing generally lower than infection
  - Synthetic growth medium
  - No host immune cells, antibodies, protein, complement
  - Static, not dynamic drug concentrations
- **Due to testing variabilities, the inherent error of MIC testing is ± 1 dilution**

  - i.e. a reported MIC of 2 µg/mL may actually be 1 of 4 µg/mL



So why do we still use MICs,

….is there something better?

MIC are still used because they are:

- Simple
- Reproducible with standardized methods
- Can be easily related to pharmacokinetic data (µg/mL)
- Withstood the *test of time*

Antimicrobial susceptibility interpretation

Breakpoints reported for MICs (S, I, R)

- **Susceptible (S)**
  - Isolate will be inhibited by typically achievable concentrations of antimicrobial agent when the dosage recommended for the site of infection is used
  - Clinical efficacy is likely
- **Susceptible dose-dependent (S-DD)**
  - Susceptibility is dependent on the dosing regimen used
  - In order to achieve higher drug exposures, higher or more frequent dosing is needed
- **Intermediate (I)**
  - Implies response rate may be lower- MIC is near resistance breakpoint
  - Isolate may be treatable in some body sites where drug exposure is higher
- **Area of technical uncertainty (ATU)**
  - Uncertainty in interpretation- further testing with other methods are needed to confirm susceptibility
- **Resistant (R)**
  - Isolate will not be inhibited by typically achievable concentration of antibiotic with recommended doses at the site of infection
  - Clinical efficacy is uncertain or less likely
- **Nonsusceptible (NS)**
  - Category used for isolates for which only susceptible breakpoint is designated because resistance is rare

william wright @wfwrighID · Feb 8

#IDTwitter #SIDPharm #Microbiology

#AMRrounds @Bornmann_CR @liunezolid called about this laboratory confirmed isolate (AMR step 1) associated with a clinically confirmed infection regarding the mechanism of resistance.

Susceptibility	Klebsiella pneumoniae complex (1) SUSCEPTIBILITY/INTERP	
Amikacin	<=8 ug/mL	S
Amoxicillin-Clavulanate	8/4 ug/mL	S
Ampicillin	>16 ug/mL	R
Ampicillin-Sulbactam	>16/8 ug/mL	R
Aztreonam	<=2 ug/mL	S
Cefazolin	>16 ug/mL	R
Cefepime	<=1 ug/mL	S
Cefoxitin	<=4 ug/mL	S
Ceftazidime	<=2 ug/mL	S
Ceftriaxone	<=1 ug/mL	S
Cefuroxime	<=4 ug/mL	S
Ciprofloxacin	<=0.25 ug/mL	S
Ertapenem	<=0.25 ug/mL	S
Gentamicin	<=2 ug/mL	S
Meropenem	<=0.5 ug/mL	S
Nitrofurantoin	64 ug/mL	I
Piperacillin-Tazobactam	>64/4 ug/mL	R
Tetracycline	>8 ug/mL	R
Tobramycin	<=2 ug/mL	S
Trimethoprim-Sulfamethoxazole	<=0.5/9.5 u...	S

We will go into more detail in subsequent lecture regarding resistance mechanisms

william wright @wfwrighID · Feb 8

Replying to @wfwrighID

Your answer to our proposed mechanism of resistance would be:

TEM-1 over-expression	24.5%
SHV-1 over-expression	31.3%
IRT type beta-lactamase	**37%**
Other (please reply)	7.2%

208 votes · Final results

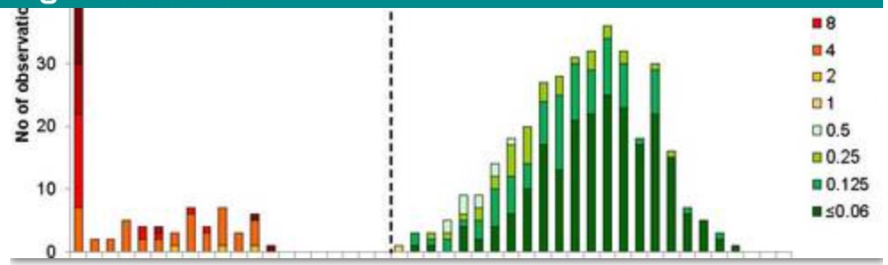
Who sets breakpoints?

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

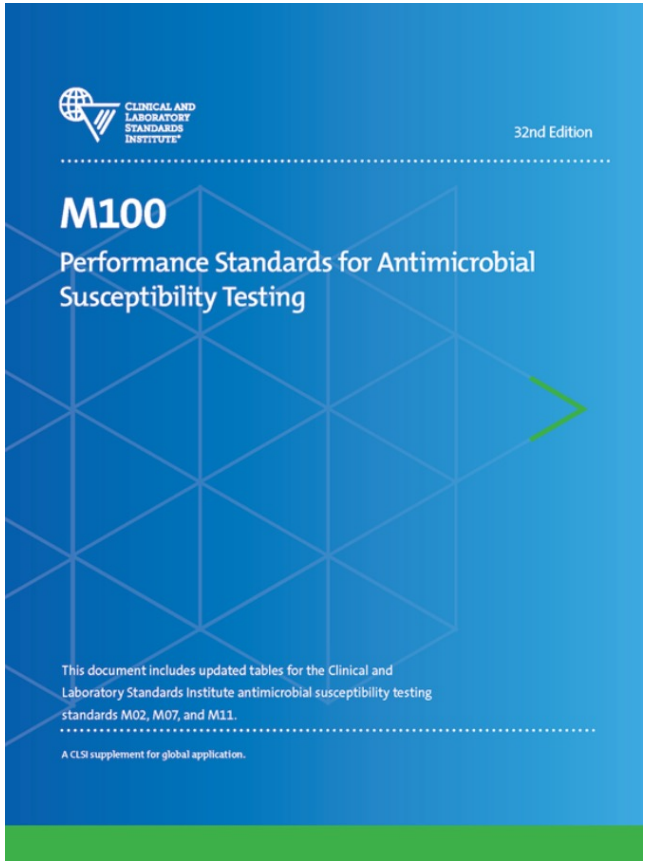
Clinical breakpoints and dosing of antibiotics

- Organization
- Consultations
- EUCAST News
- New definitions of S, I and R
- Clinical breakpoints and dosing
  - About "Clinical breakpoints".
  - Rationale documents



Clinical breakpoints - breakpoints and guidance

January 2, 2023

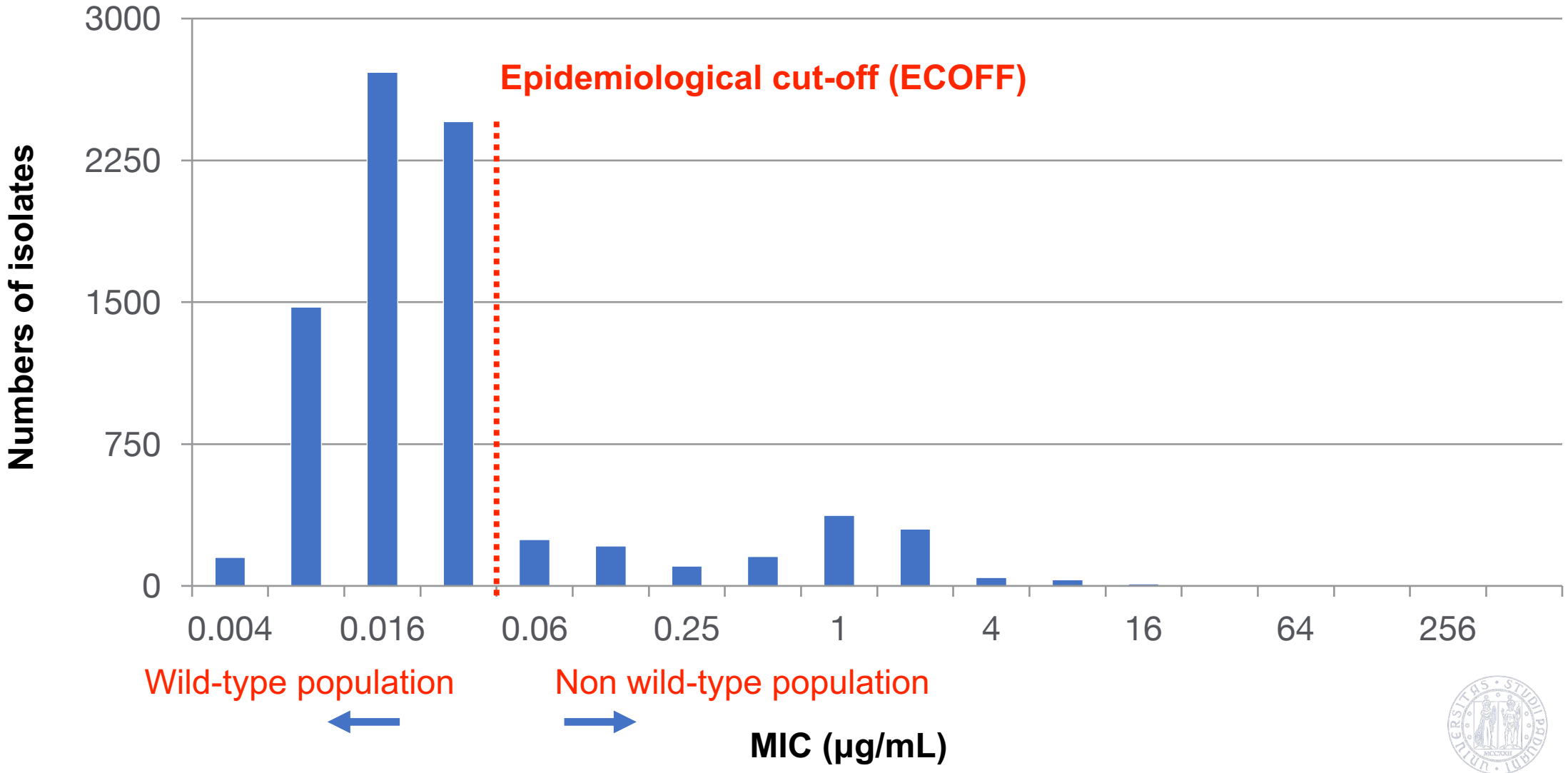


FDA U.S. FOOD & DRUG ADMINISTRATION

FDA in United States, but generally follows CLSI breakpoints

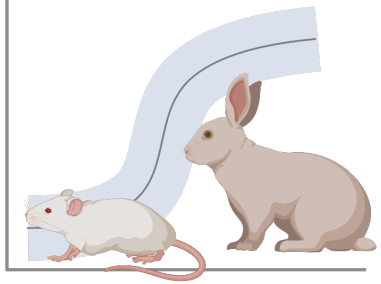
What information is used to set breakpoints?

MIC distributions from testing large numbers of isolates

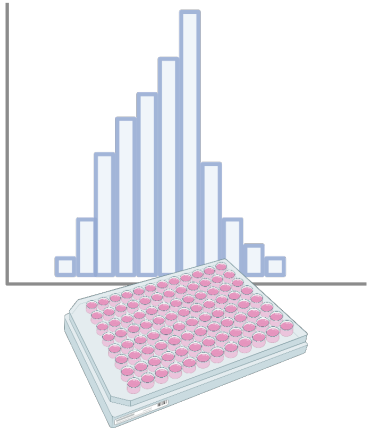


What other data is used to set breakpoints?

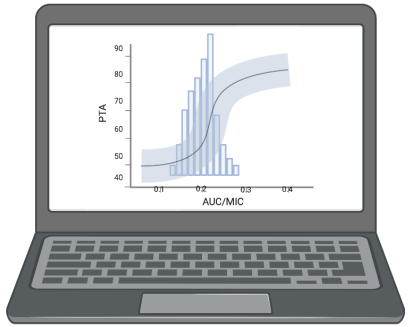
PK/PD targets



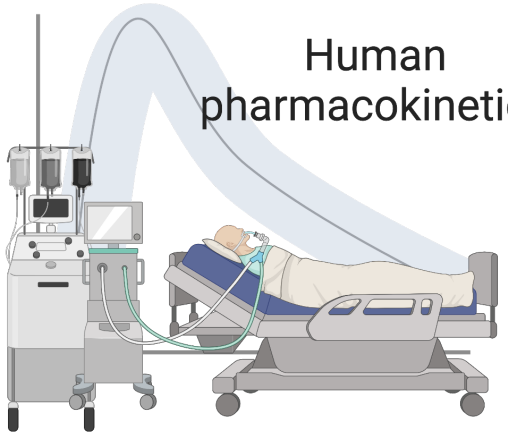
MIC distributions



Simulation and prediction

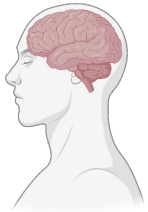


Human pharmacokinetics



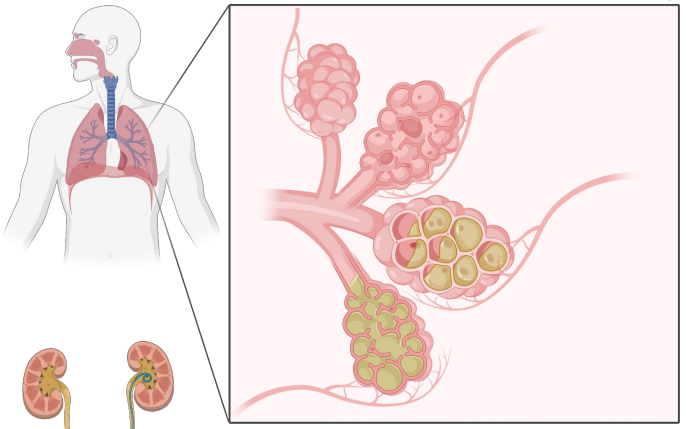
Clinical outcome

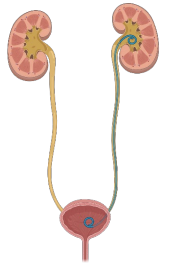
Disease-specific pharmacokinetic



(e.g., meningitis)

(e.g., pneumonia, bloodstream infection)





(e.g., urine)

Antibiotic breakpoints

Establishing clinical correlation-general rule of thumb

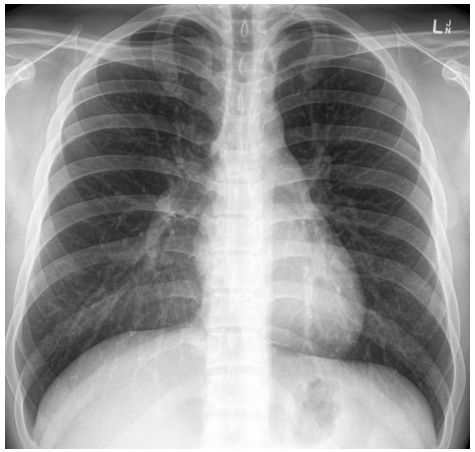
90/60 rule

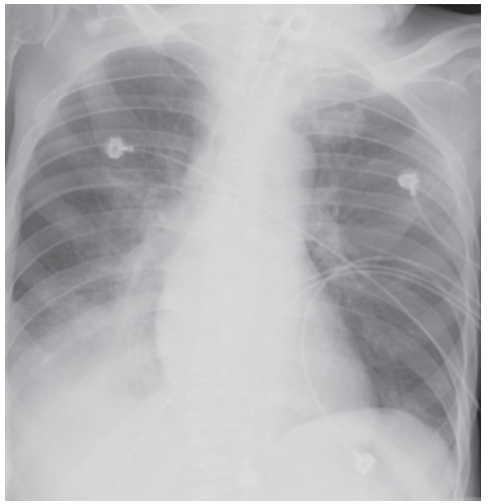
“Susceptible” ≥ 90% clinical response
“Resistant” ≤ 60% clinical response

Susceptibility report/ antibiograms

Sputum culture: *P. aeruginosa*

Antibiotic	Interpretation
Aztreonam	S
Ceftriaxone	R
Cefepime	S
Ciprofloxacin	I
Gentamicin	S
Meropenem	S
Pipercillin/tazobactam	S





Cumulative susceptibility reports/ institutional antibiograms

% Susceptible of tested isolates

Drug	Acinetobact.	E. coli	E. cloacae	K. pneumoniae	P. aeruginosa
Amikacin	89	99	99	99	92
Aztreonam		92	84	95	56
Cefepime	61	94	97	95	57
Ceftazidime		95	86	95	78
Imipenem	92	100	100	100	78
Meropenem		100	97	100	78
Pip/Tazo		94	76	91	85
Ciproflox	79	55	93	95	65
Levoflox		54	94	95	65

What about combination antimicrobial therapy?

Combination antimicrobial therapy

- **Most infections in patients with "normal" host defenses can be treated with a single antimicrobial agent**
  - Provided highly effective monotherapy is used-i.e. β-lactams
- **Combinations may provide broader-spectrum of coverage or pharmacokinetic advantages in select situations**
- **Combination therapy standard of care for some bacterial infections**
  - e.g., tuberculosis, enterococcal endocarditis
- **Combination therapy may be desirable for more resistant pathogens where single high-potency antibiotic with ideal pharmacokinetics are lacking (e.g., *Acinetobacter* spp.)**

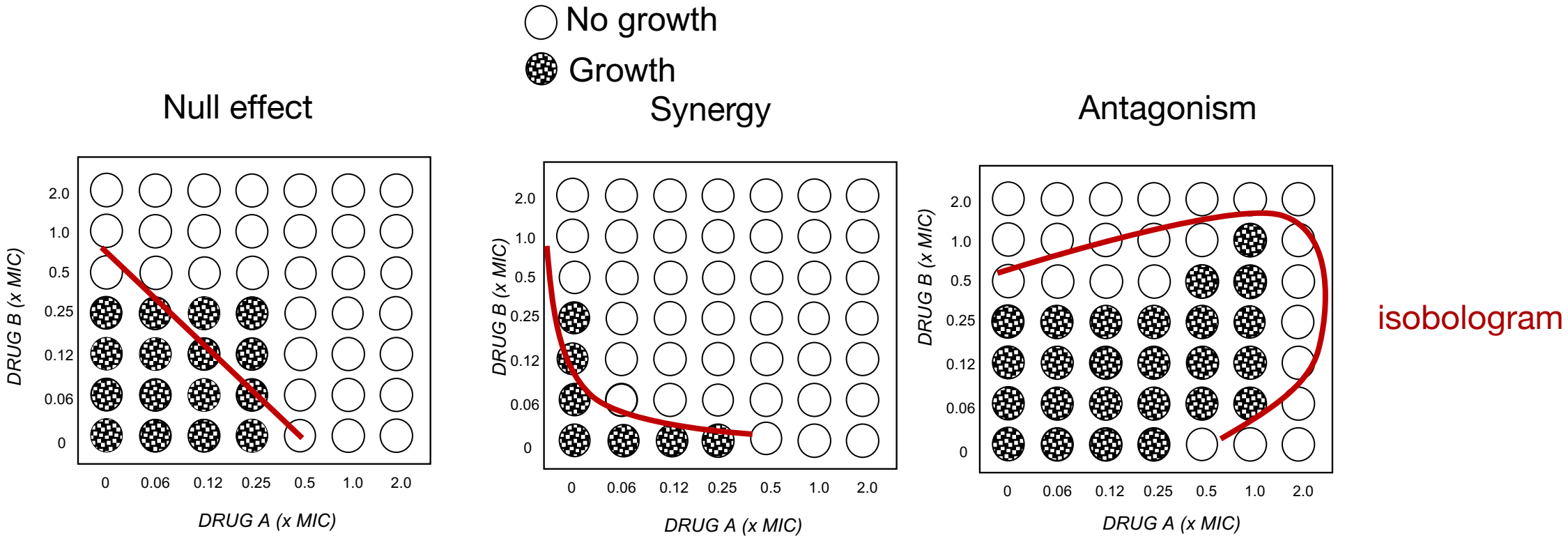
Antimicrobial interactions

	Combined Antimicrobial Effects		
Interaction model	**Less than expected sum effects**	**Same as expected sum effects**	**More than expected sum effects**
Loewe additivity (similar modes of action or pathways	Antagonism	Additive	Synergy
Bliss independence (independent modes of action or pathways)	Antagonism	Indifferent	Synergy

Greco WR et al. *Pharmacol Rev* 1995;47:331

How can combination therapy be tested in the laboratory?

Checkerboard test



isobologram

$$\frac{MIC_a + MIC_b}{MIC_a} = \mathrm{FIC_a}$$

$$\frac{MIC_b + MIC_a}{b} = \mathrm{FIC_b}$$

$$\boldsymbol{FIC_a + FICb = FIC\ Index\ (FICI)}$$

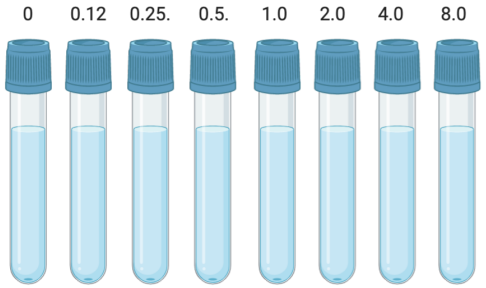
FICI $< 0.5 =$ *Synergy*
FICI 0.5-4 $=$ *Additive or null interaction (Loewe)*
FICI > 4 *Antagonism*

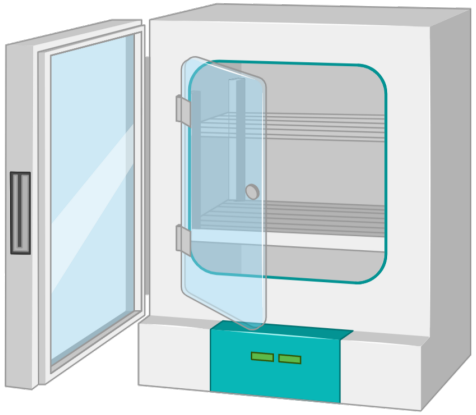
Synergy testing
time-kill curves

Multiples of MIC

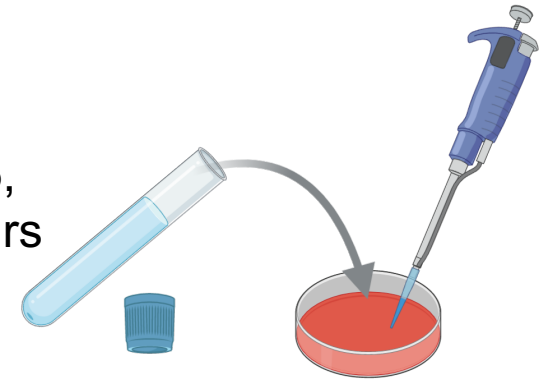
Incubate for 24h at 35°C

Standardized inoculum of bacteria in each tube + Serial dilutions (multiples of MIC) of antibiotic





Sample tubes at 0, 0.5, 1,2,4,8, 12 and 24 hours



incubate

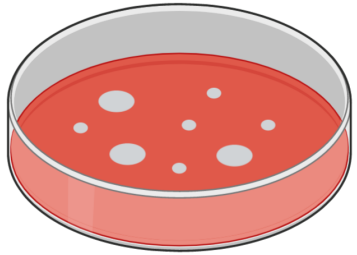


Plate of microbiological agar, incubate for 24 hours

Count number of viable colony forming units (CFU) on each plate

Synergy testing
time-kill curves

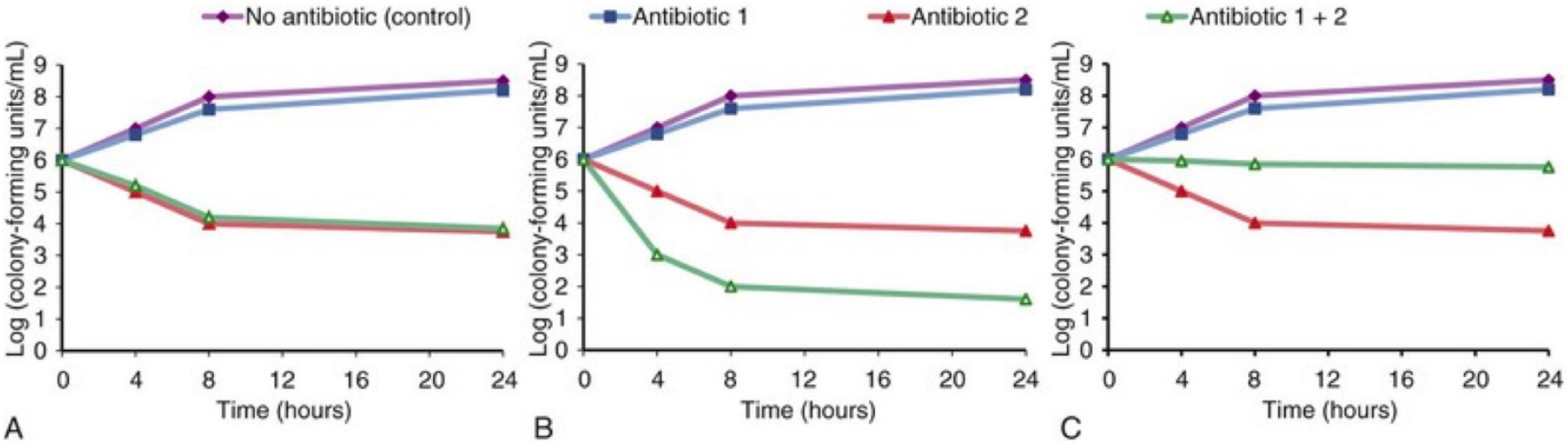
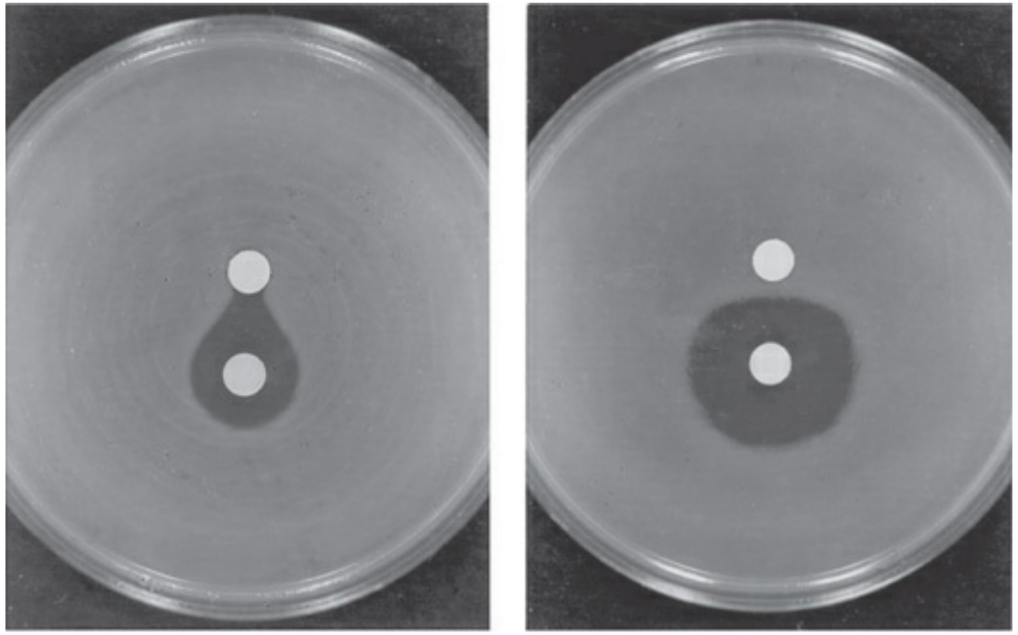
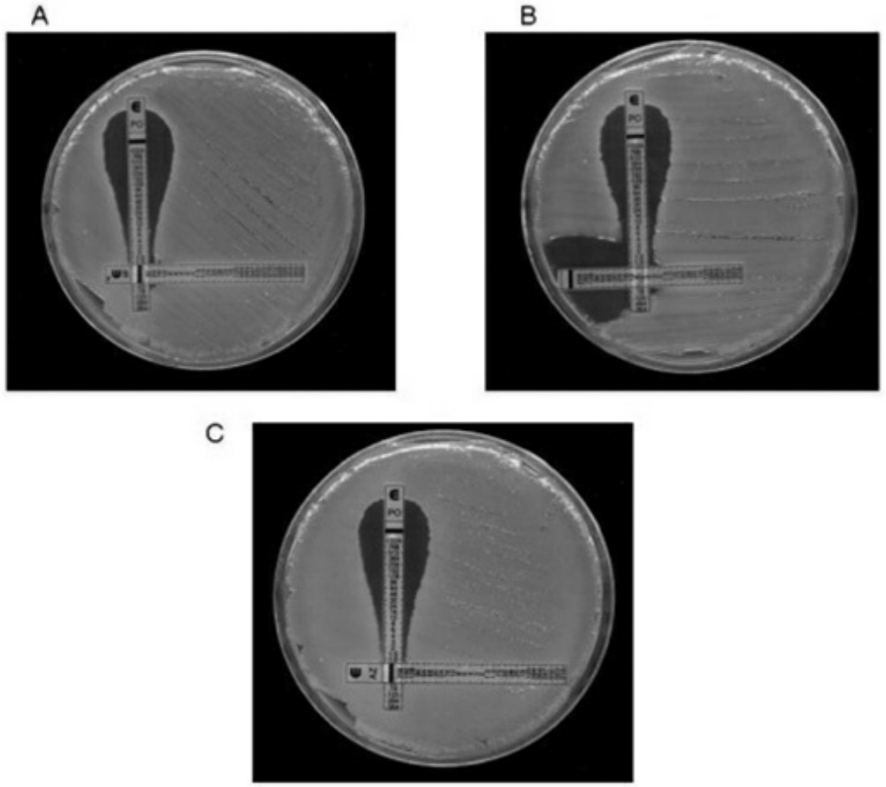


FIGURE 17-1 **Antibacterial effects of antibiotic combinations.** **A,** The combination of antibiotics 1 and 2 is indifferent (killing by antibiotic 2 is unchanged when antibiotic 1 is added). **B,** The combination of antibiotics 1 and 2 results in synergy (killing by antibiotic 2 is significantly enhanced when antibiotic 1 is added at a subinhibitory concentration). **C,** The combination of antibiotics 1 and 2 is antagonistic (killing by antibiotic 2 is diminished in the presence of antibiotic 1).

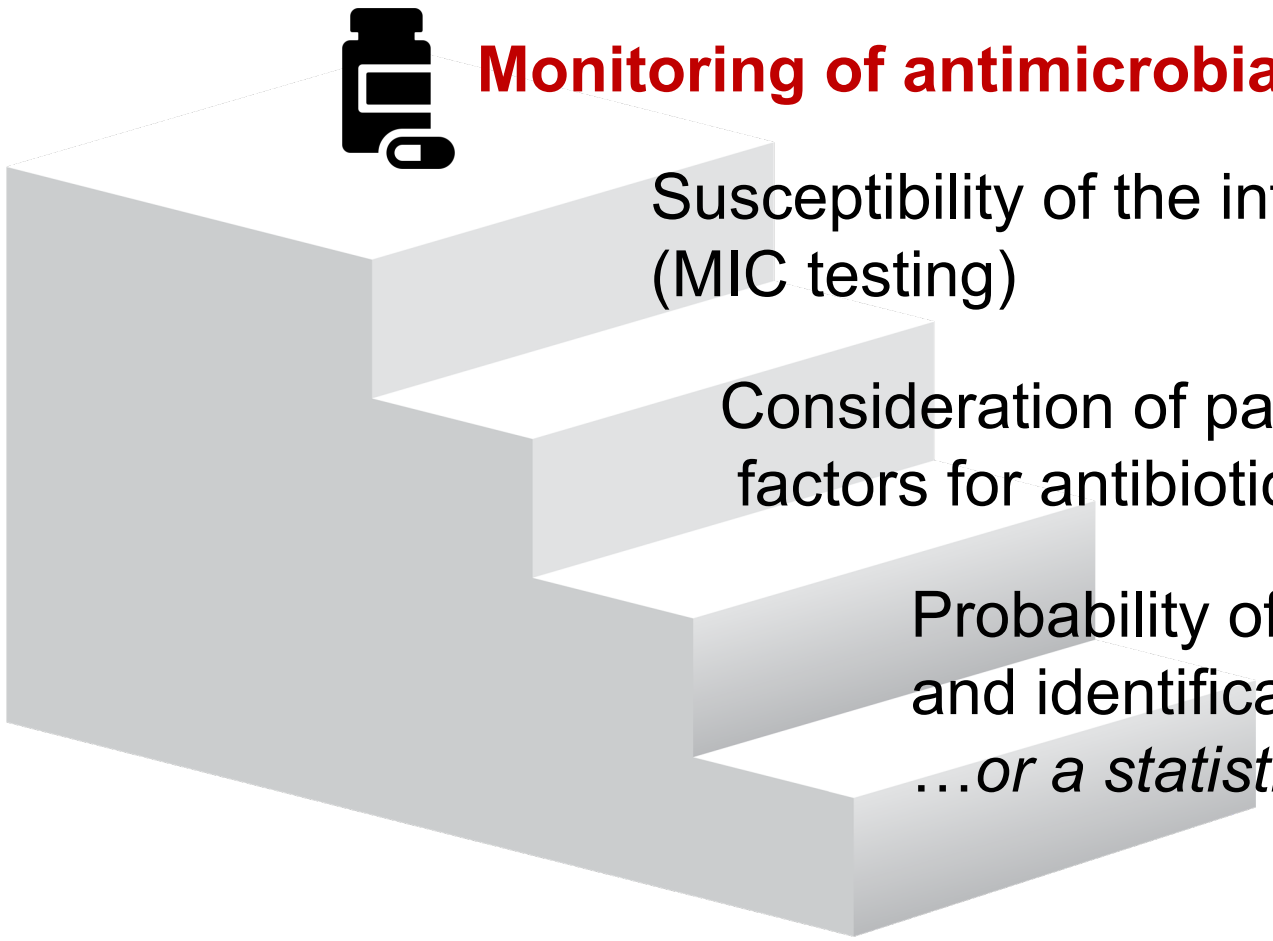
Principles of Antibiotic Therapy. Eliopoulos and Moellering. Mandell, Douglas and Bennet 8th Edition

Synergy testing
agar based methods





Amsterdam, Daniel. Antibiotics in Laboratory Medicine .
6th Edition. Wolters Kluwer Health.



Monitoring of antimicrobial therapy

Susceptibility of the infecting organism (MIC testing)

Consideration of patient-specific factors for antibiotic therapy

Probability of infection (differential dx) and identification of the infecting organism

…*or a statistically reasonable guess*

Monitoring antimicrobial therapy

- Is the patient improving?
- Can the antibiotics be converted from IV to oral?
- Can the antibiotics be narrowed to a specific pathogen?
  - After culture and sensitivity (MIC) results are returned
- Should therapeutic drug monitoring (TDM) be performed?
- Is kidney and liver function stable?
- Is the patient experiencing side effects from the antibiotic?

Therapeutic drug monitoring (TDM)
General recommendations

- **Standard of care:**
  - **To reduce risk of nephrotoxicity, ensure efficacy:**
    - Aminoglycosides (gentamicin, tobramycin, amikacin)
    - Glycopeptides (vancomycin, teicoplanin)
- **Emerging recommendations:**
  - **Ensure efficacy, reduce risk of toxicity in critically-ill patients**
    - Beta-lactams, linezolid

This will be addressed in more detail subsequent lectures

Abdul-Aziz MH et al. Intensive Care Med. 2020;46:1127-1153.

Monitoring antimicrobial therapy

- Is the patient improving?
- Can the antibiotics be converted from IV to oral?
- Can the antibiotics be narrowed to a specific pathogen?
  - After culture and sensitivity results are returned
- Should therapeutic drug monitoring (TDM) be performed?
- Is kidney and liver function stable?
- Is the patient experiencing side effects from the antibiotic?

Common antibiotic adverse effects

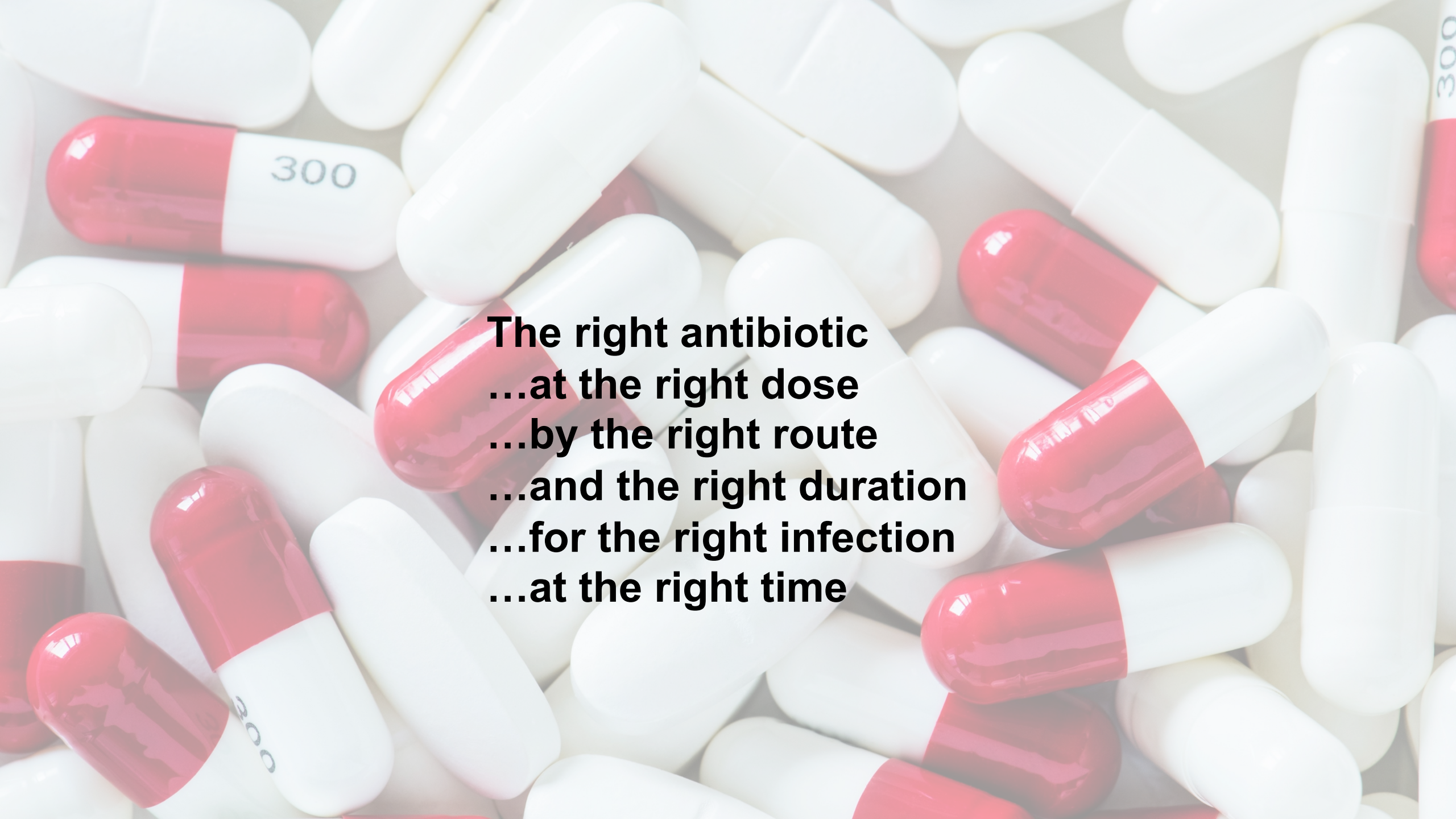
Subjective	Objective
• GI disturbance • Flushing • Rash • Pain at cannulation site • Altered mood • Headache • Joint pain • Muscle pain • Taste disturbance • Numbness and tingling	• Fever • Renal injury • Hyperkalemia • Cholestasis • Hepatitis • Neutropenia • Thrombocytopenia • Prolonged QT interval • Ototoxicity

Common reasons for antibiotic failure

- Too short of duration (compliance)?
- Incorrect diagnosis?
- Incorrect antibiotic dose for diagnosis and pathogen
- Lack of source control (e.g., drainage of abscess)
- Emergence of resistance
- Patient has new (super)infection

Summary

- Antibiotic therapy is often started empirically based on knowledge of which organisms typically cause infection against which the treatment will be directed
- The choice of therapy must consider site of infection, patient allergy history, age, organ function, and other patient-specific factors to minimize adverse effects
- Once the pathogen is identified and susceptibility is known, therapy should be tailored the the narrowest required spectrum and shortest duration of therapy administered by mouth when feasible



The right antibiotic
…at the right dose
…by the right route
…and the right duration
…for the right infection
…at the right time

Principles of Antibiotic Therapy
Part 2. Antibiotic PK and Dosing Optimization

Russell E. Lewis

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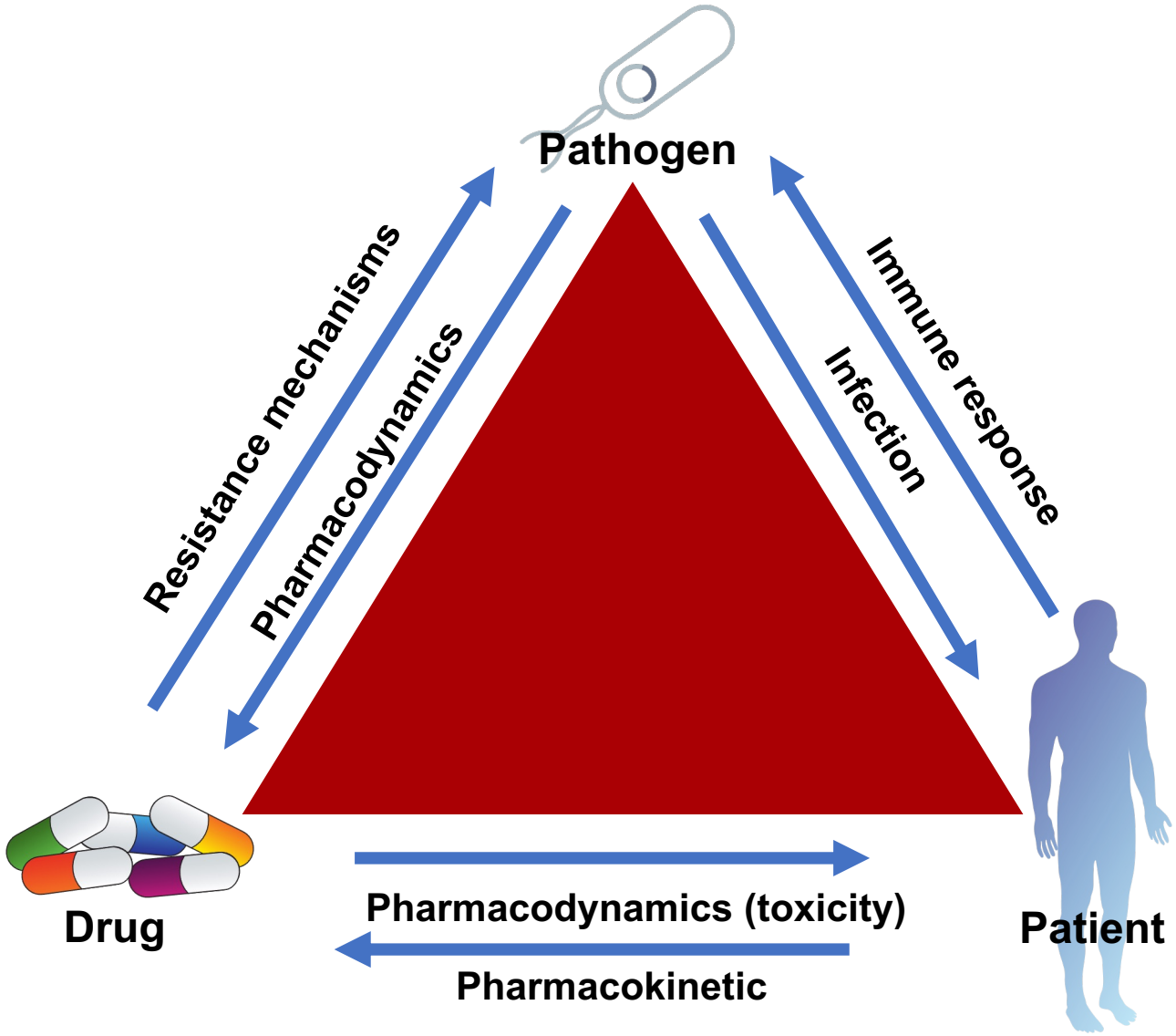
UNIVERSITÀ
DEGLI STUDI
DI PADOVA

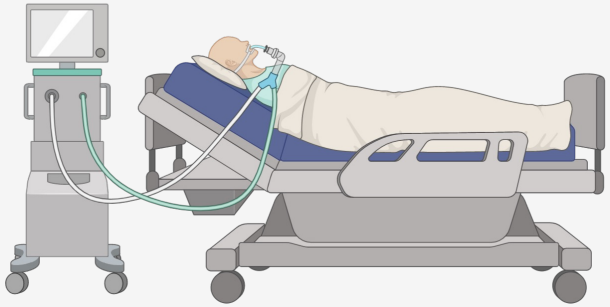
MEP9085779 (AA 2022/2023)

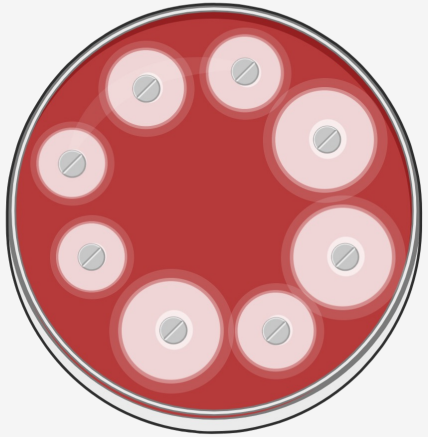
28 Feb 2023

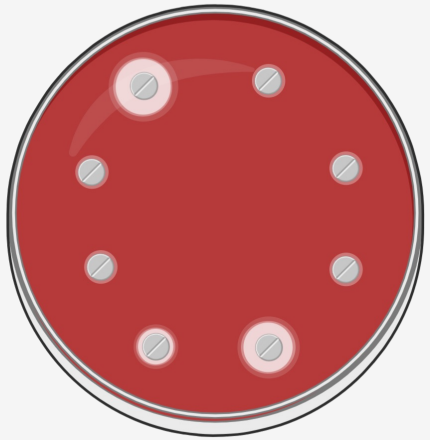
Pharmacology of antimicrobial therapy



Altered pharmacokinetics and antibiotic resistance travel together



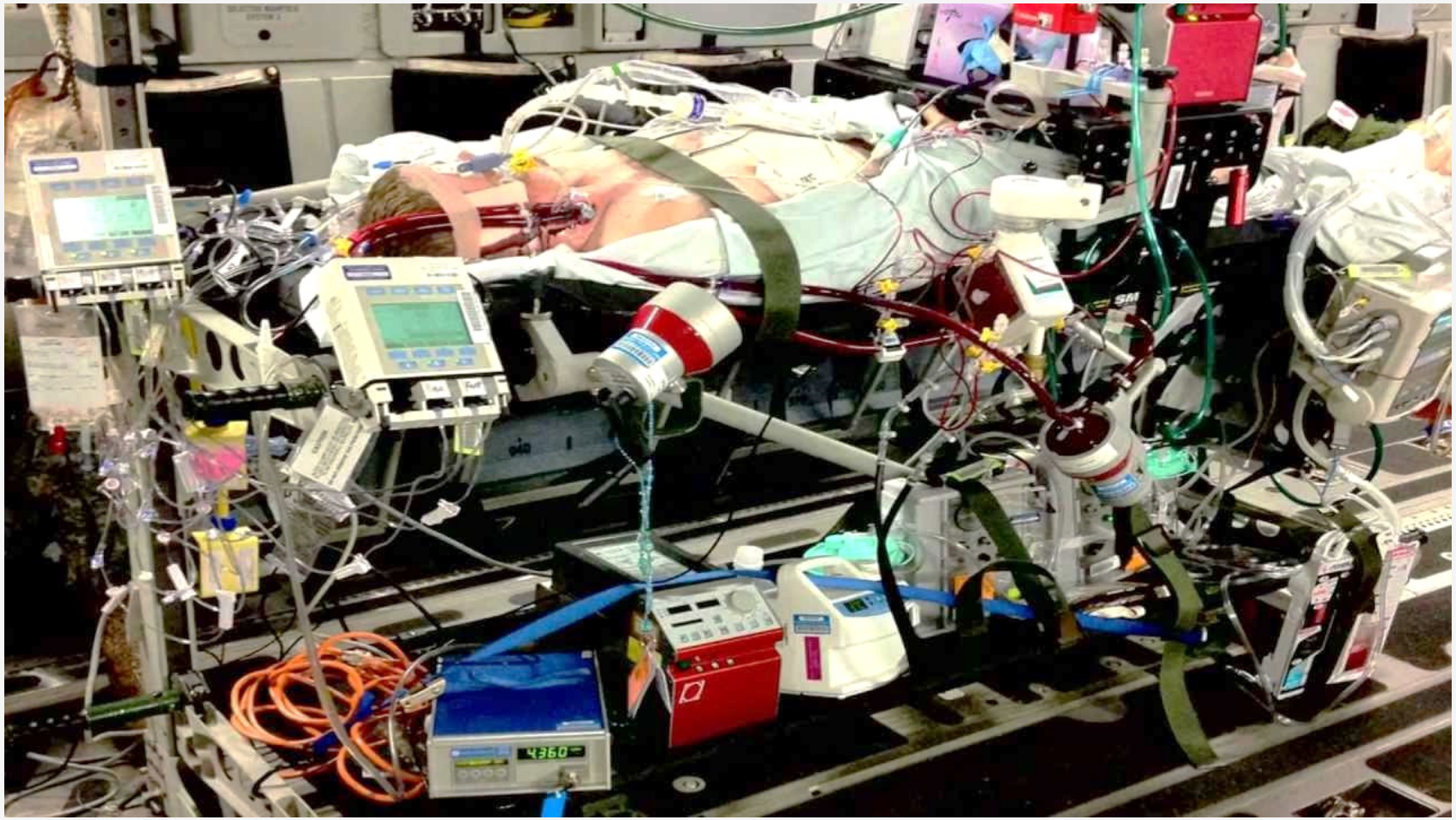




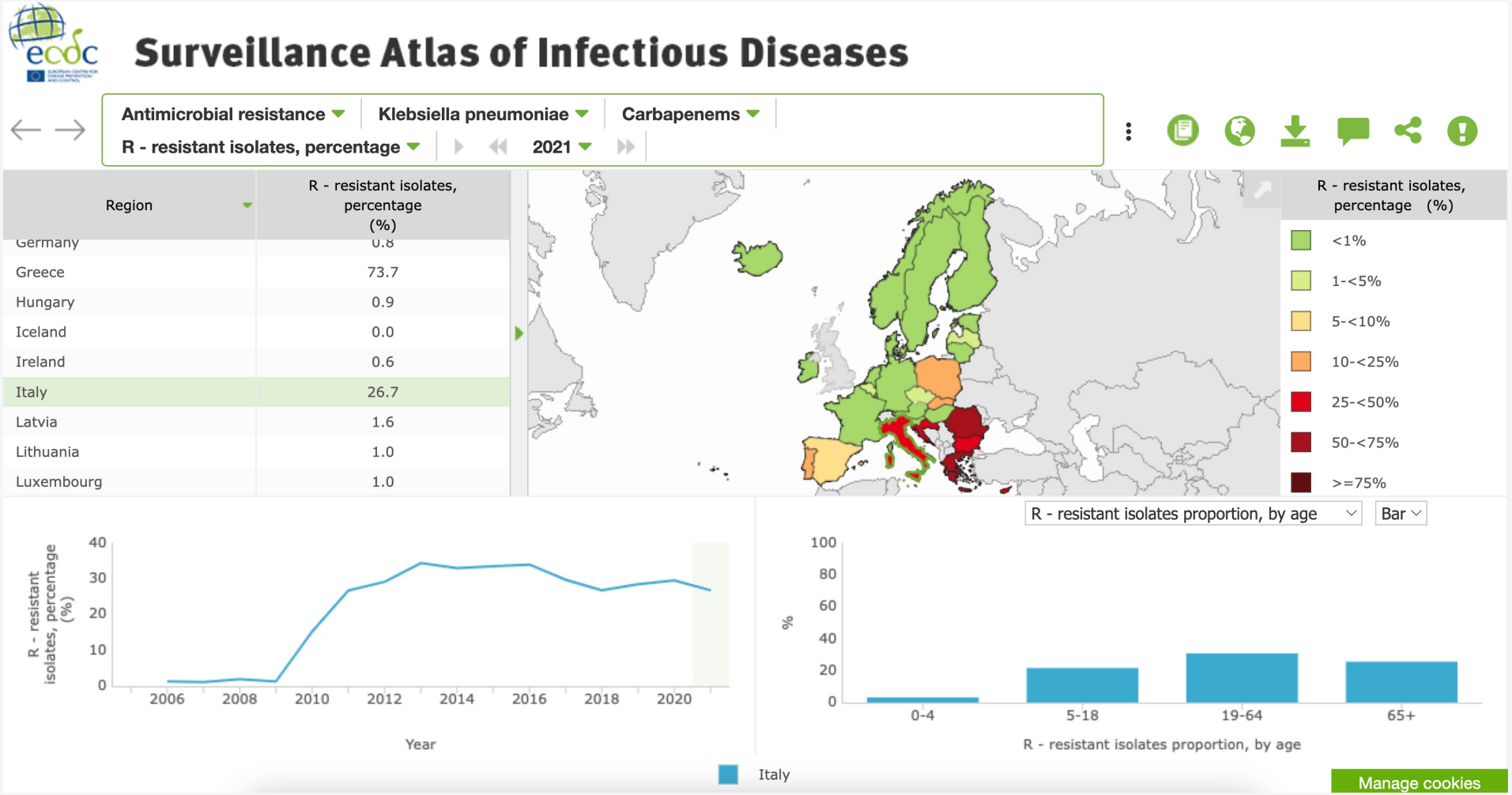
Less severely ill,
highly susceptible bacteria

More severely ill,
multi-drug resistant bacteria

Different antibiotic dosing strategies will be needed depending on the MIC and the patient



As a physician in Italy, you will frequently encounter multi-drug resistant bacteria



Source: EARS-NET: http://atlas.ecdc.europa.eu/public/index.aspx

Why knowledge of antimicrobial PK/PD is important

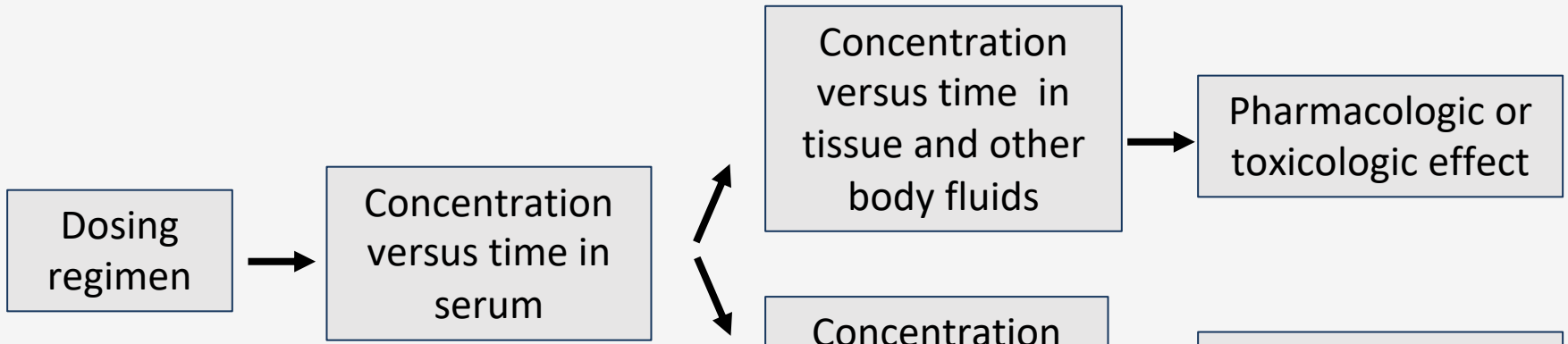
- Antimicrobial resistance
- Registration trials for antibiotics generally exclude very sick patients with infections caused by resistant pathogens → dosages in drug labeling rarely correct for critically-ill patients
- Pharmacokinetic variability can be extreme from one patient to the next-no “one size fits all” dosing

Antibiotic dosing and selection are variables that you can directly control to improve patient outcomes

Outline

- Why knowledge of PK/PD principles is essential for antibiotic dosing
- Core PK/PD concepts for antibiotics
- Practical application of PK/PD dosing principles for antibiotics

Pharmacology of antimicrobials



Absorption
Distribution
Metabolism
Elimination

Pharmacokinetics
"PK"

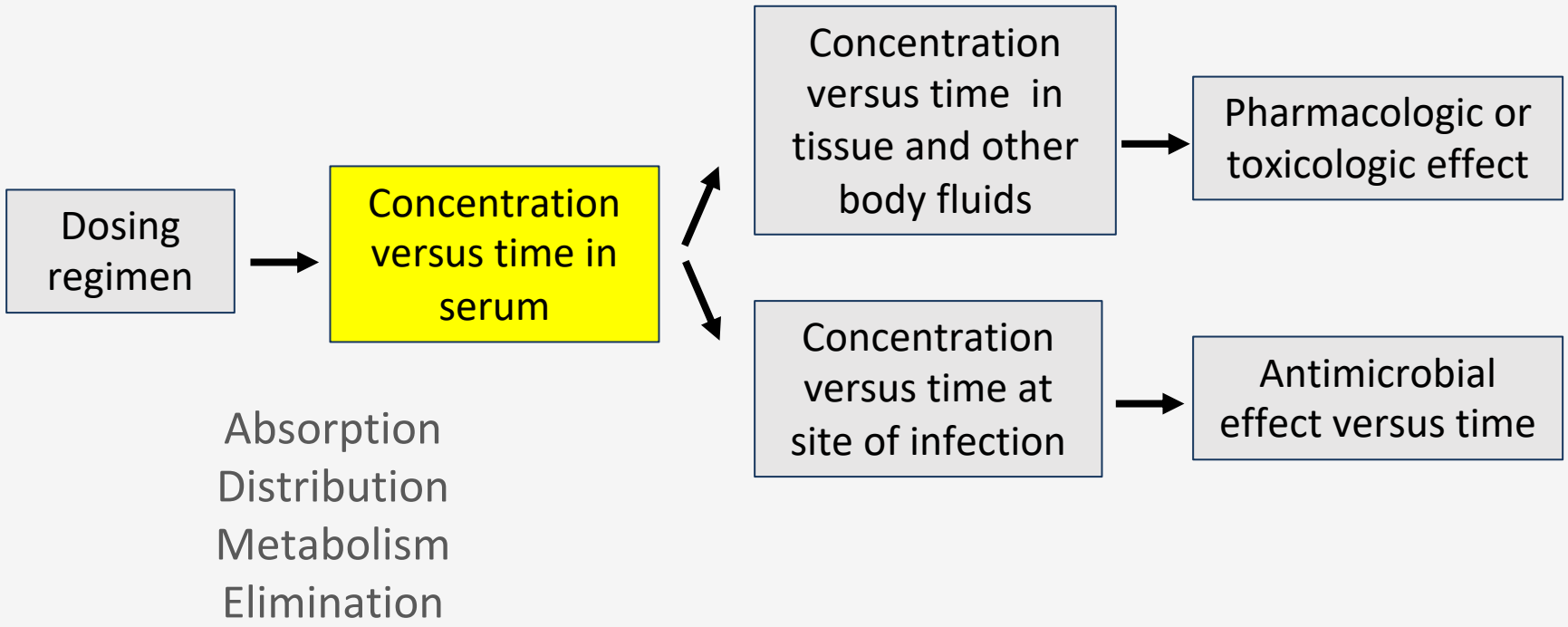
What the body does to drug

Pharmacodynamics
"PD"

What the drug does to the body (and bacteria)

Craig WA. Clin Infect Dis 1998;26:1-12.

Pharmacology of antimicrobials



Pharmacokinetics
"PK"

What the body does to drug

Pharmacodynamics
"PD"

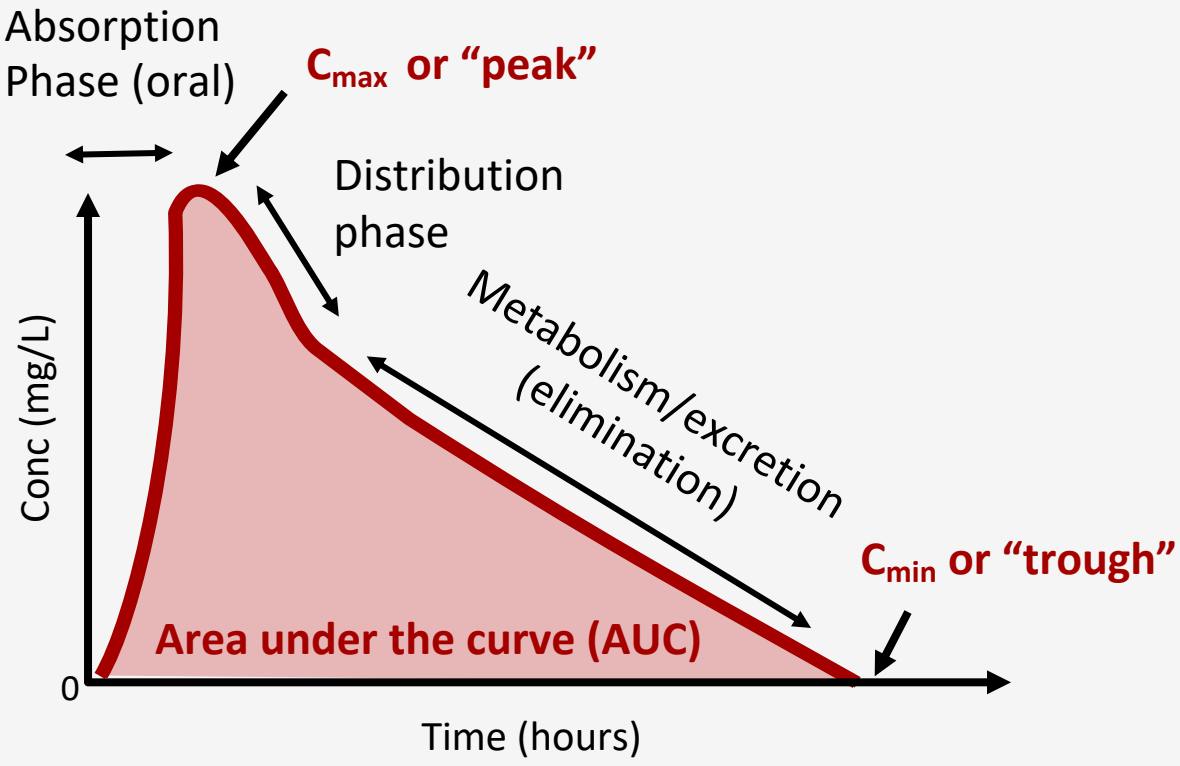
What the drug does to the body (and bacteria)

Craig WA. Clin Infect Dis 1998;26:1-12.

Antibiotics pharmacokinetics are described by concentration-time curves in serum

Antibiotic dose → Concentration versus time in serum

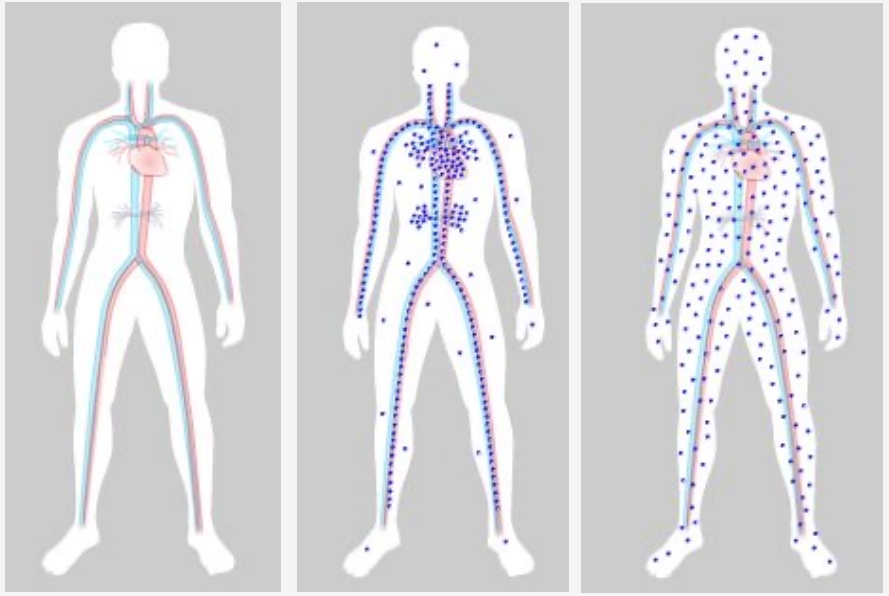
Absorption
Distribution
Metabolism
Elimination



Craig WA. Clin Infect Dis 1998;26:1-12.

Key PK variable #1 –Volume of distribution (Vd)

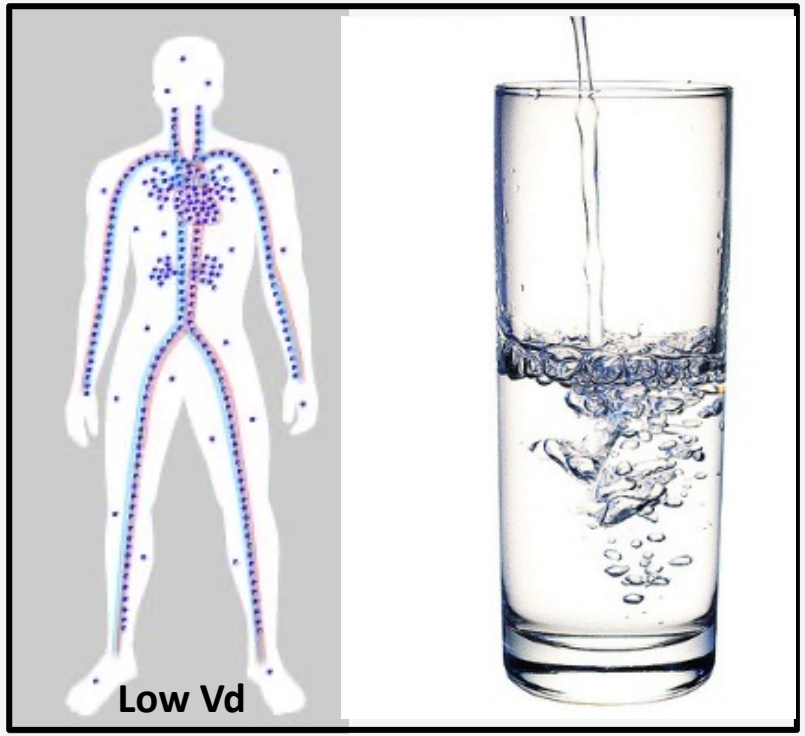
- **The volume which appears to hold the drug if it was present in the body at the same concentration found in plasma**
  - It is estimated, not directly measured
  - Reported in liters (L) or liters per kilogram (L/kg)
  - Average plasma volume in adults is approximately 3 L



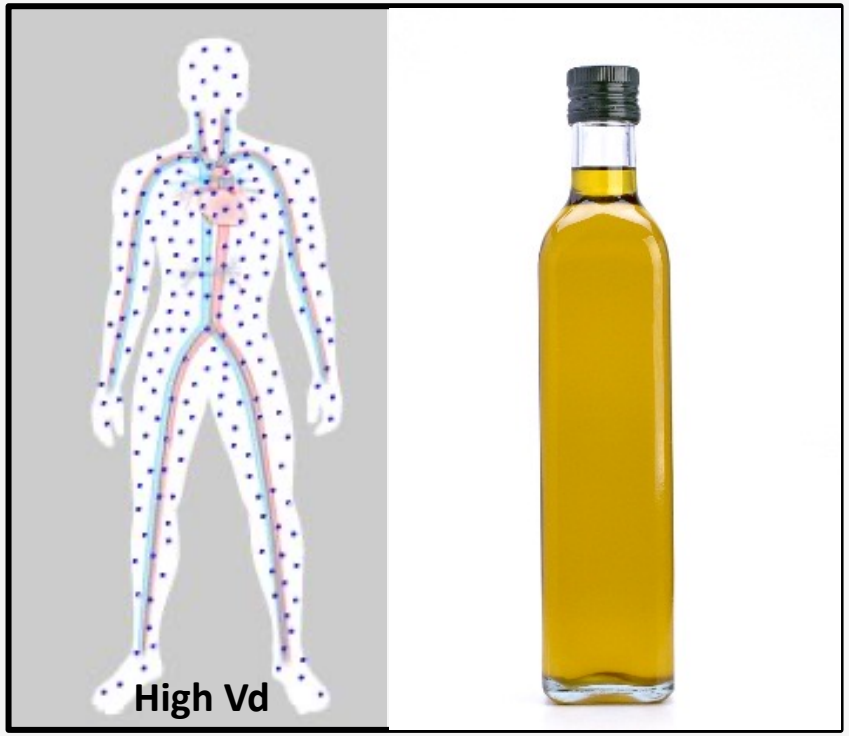
Before dose Low Vd High Vd

Key PK variable #1 –Volume of distribution (Vd)

- Volume of distributed is affected by the physiochemical properties of the drug
- **Factors that favor low Vd:** high water solubility, high protein binding, decreased tissue binding → converse is also true



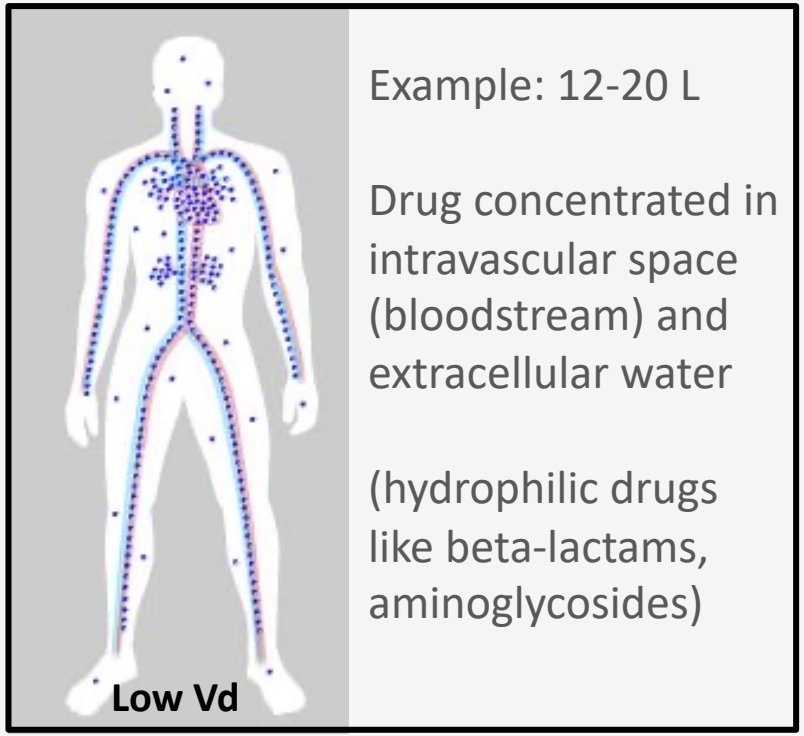
Hydrophilic



Lipophilic

Key PK variable #1 –Volume of distribution (Vd)

Provides information on how much antibiotic is distributed in tissues vs. plasma → some clinical relevance

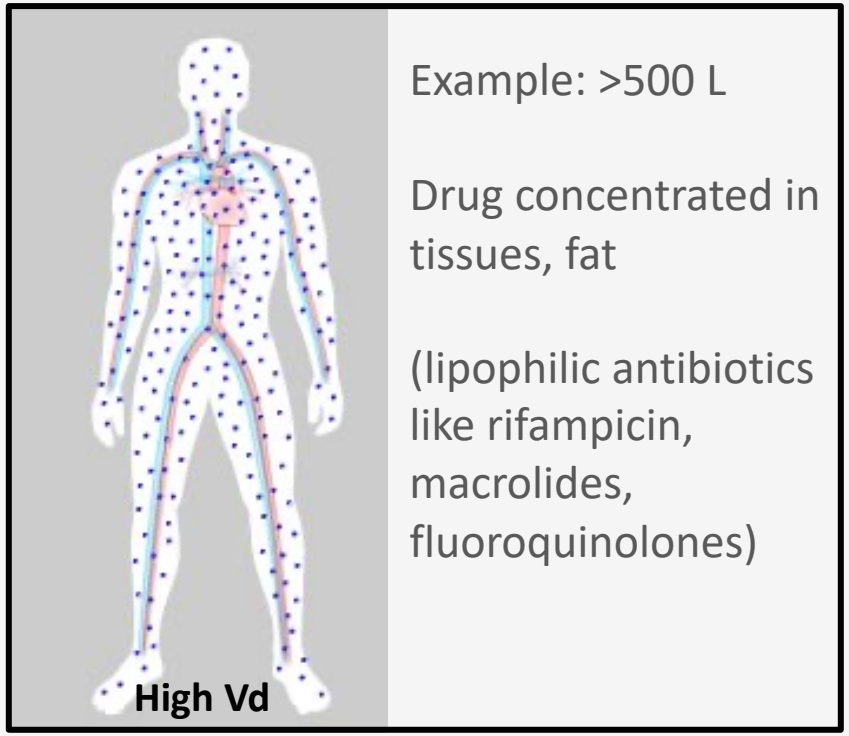


Example: 12-20 L

Drug concentrated in intravascular space (bloodstream) and extracellular water

(hydrophilic drugs like beta-lactams, aminoglycosides)

Bloodstream > tissue sites



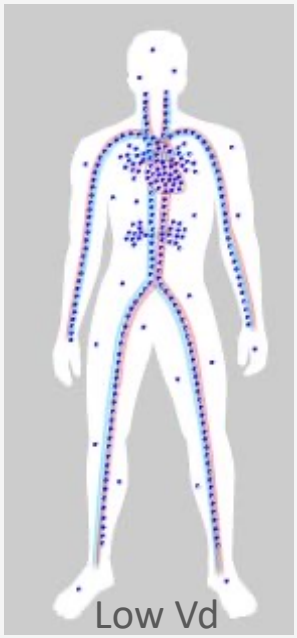
Example: >500 L

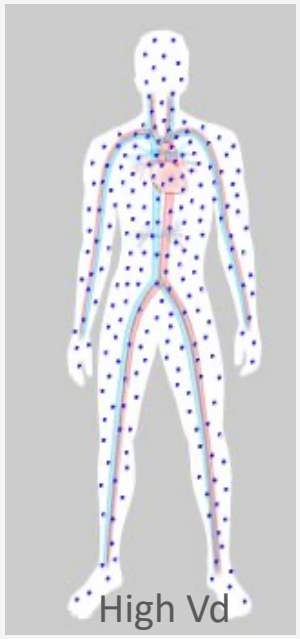
Drug concentrated in tissues, fat

(lipophilic antibiotics like rifampicin, macrolides, fluoroquinolones)

Tissue > bloodstream

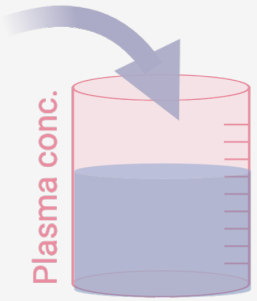
Another way to think of volume of distribution

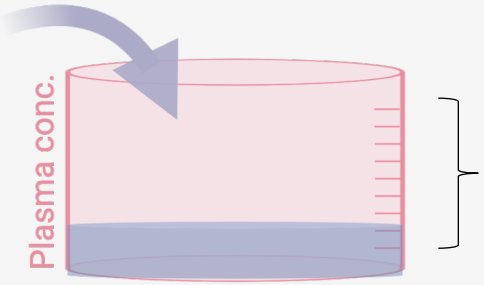




Same amount of drug “poured in” body, but different drugs and different patients have different beaker sizes

Fixed antibiotic dose (i.e. 100 mg in 50 mL)

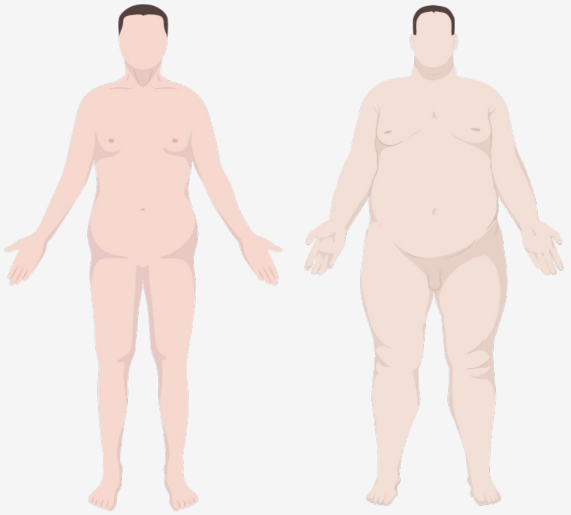




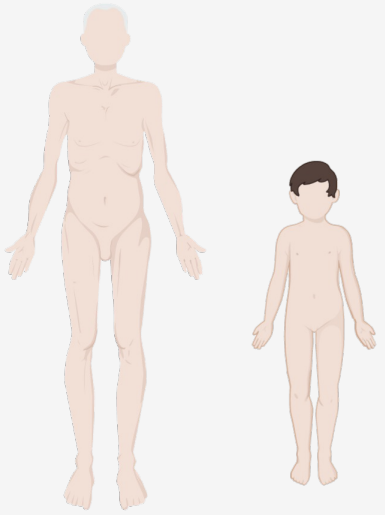
Apparent plasma concentrations

Examples of factors that affect volume of distribution (Vd)

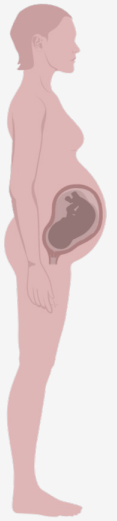
Body mass



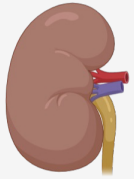
Age, Sex



Pregnancy

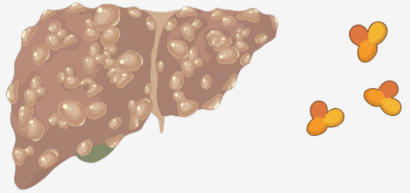


Kidney disease (e.g., uremia)



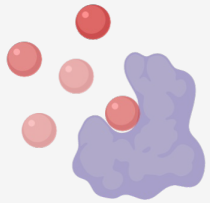
uremia decreases drug tissue binding, ↓Vd

Liver disease (e.g., cirrhosis)



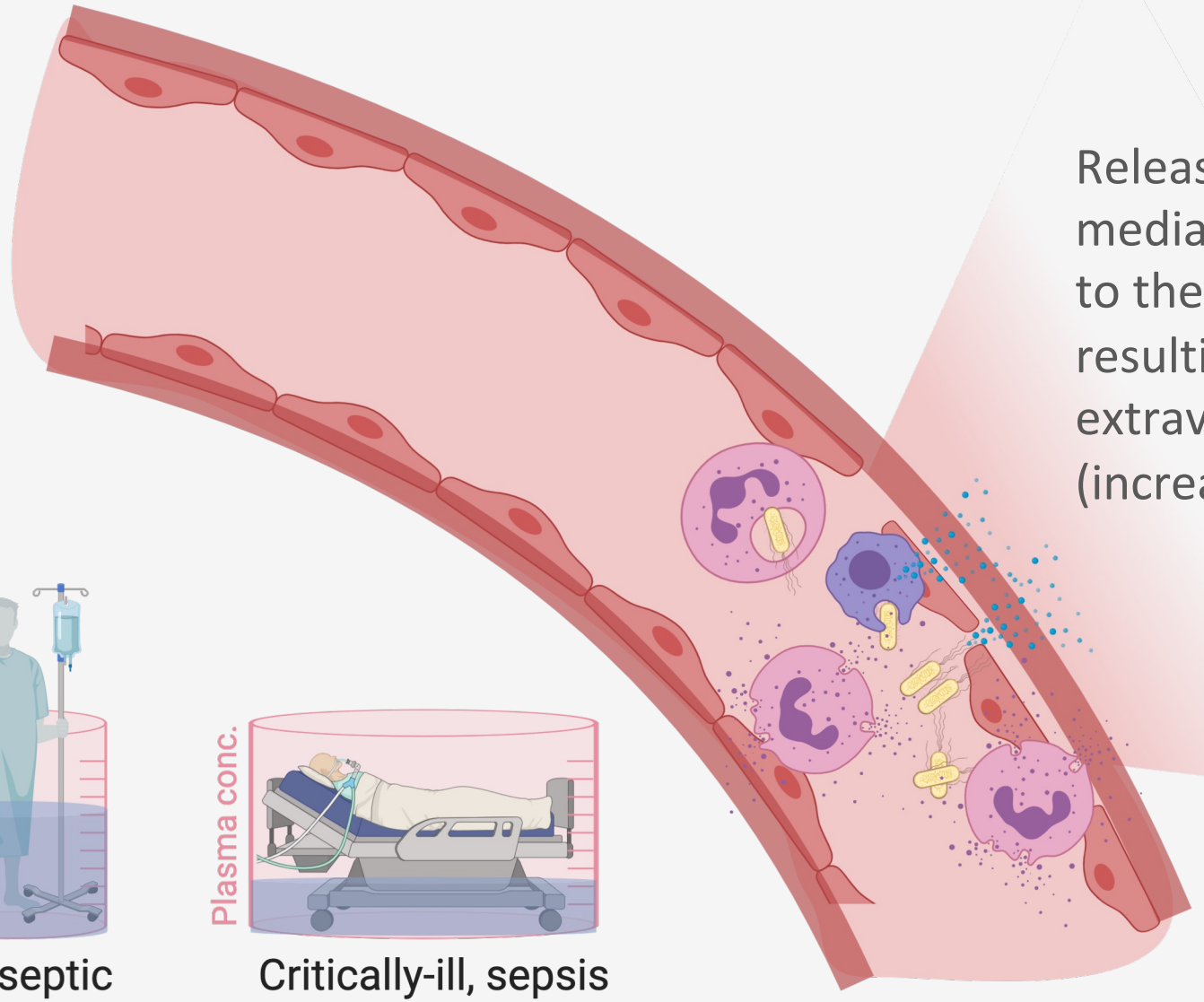
decreased protein production and binding to drugs, ↑ Vd

Drug interactions

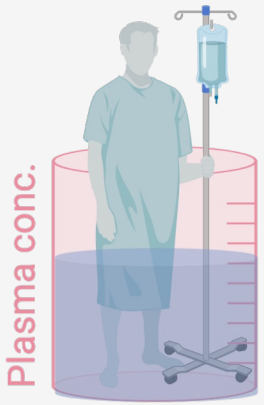


displaced protein binding of drug, ↑Vd

Sepsis alters the volume of distribution of antibiotics



Release of inflammatory mediators causes damage to the vascular endothelium, resulting in expansion of extravascular space (increased volume of distribution)



Non-septic

Critically-ill, sepsis

Apparent Vd

Key PK variable #2- Clearance

- **Drug elimination from the body**
  - Described by volume of blood removed of drug unit per time
- **Unit of measure mL/min or L/hr**
- **Clearance is affected by**
  - Patient's disease, organ function genetics, interactions with other drugs…etc.

Changes in clearance between different patients: (*inter*-individual variability, IIV)

Changes in clearance over time in the same patient: (*intra*-individual variability)

Key PK variable #2- Clearance

- **Total body clearance:**
  - $CL_{renal} + CL_{hepatic} + CL_{other}$
- Formulas for calculating antibiotic clearance can be found in the medical literature or some drug references
- May be needed in patients with complex pharmacokinetics

Example: Meropenem dosing in a critically-ill patient

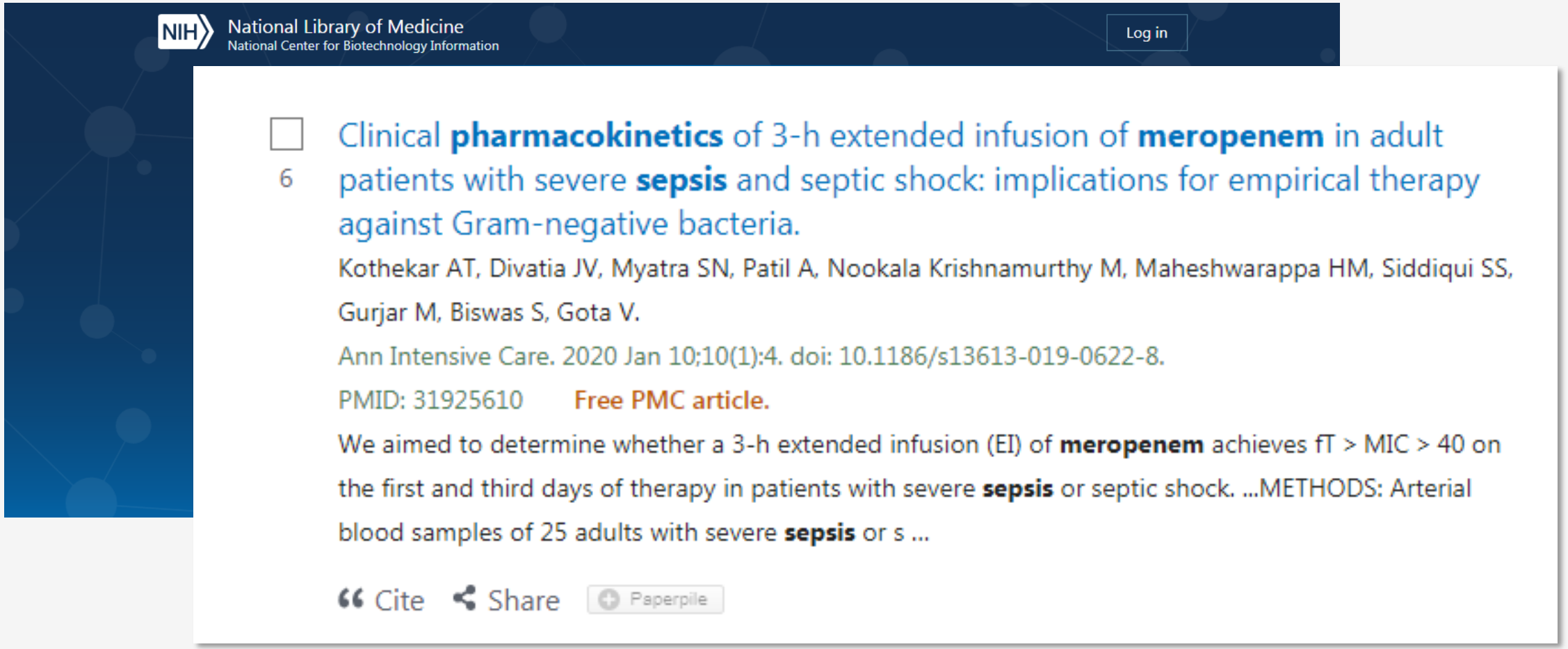


Table 3 Pharmacokinetic parameters after 3-h extended infusion (EI) of 1000 mg meropenem 8 h for first and third days

Pharmacokinetic parameters	Day 1 (first dose) ($n=24$[a])	Day 3 (seventh dose) ($n=23$[b])	Change[c] from day 1 to day 3 (%)	P[d]
Cmax (µg/mL)	15.36 ± 1.11	14.14 ± 2.02	− 7.1	NS
AUC (µg h/mL)	57.92 ± 5.98	43.82 ± 7.33	− 24.3	NS
$T_{1/2}$ (h)	1.31 ± 0.24	0.6 ± 0.23	− 54.2	0.04
Ke (1/h)	0.53 ± 0.10	1.15 ± 0.44	+ 116.1	NS
Vd (L)	32.61 ± 4.3	19.83 ± 6.13	− 39.2	NS
Cl (L/h)	17.26 ± 1.78	22.86 ± 3.82	+ 32.4	NS

All values shown as mean ± SE

Cmax maximum plasma concentration, *NS* not significant, *AUC* area under concentration–time curve, $T_{1/2}$ half-life, *Ke* elimination rate constant, *Vd* apparent volume of distribution, *Cl* total body clearance

$P < 0.05$ statistically significant

[a] One patient was withdrawn from the analysis as the blood samples were hemolyzed

[b] One patient expired before collection of day three samples

[c] (+) indicates increase and (−) indicates decrease from day 1 to day 3

[d] Paired data of 23 patients between day 1 and day 3 compared using paired *t*-test

Meropenem pharmacokinetics
(Lexi-COMP database drug reference)

Volume of distribution= 15-20 liters
Clearance= 10-13 L/h

40% ↓ change in Vd in first 3 days
32% ↑ change in Cl in first 3 days

*note: sometimes clearance may be presented as a formula when closely related to renal function or parameters:

e.g., Clearance=0.078 x Creatinine clearance + 2.85

Kothekar AT, et al. Ann Intensive Care 2020; 10:4.

Integrating volume of distribution (Vd) and clearance (CL)

- **V_d and CL are both physiologically-based**
  - A change in patient fluid status or distribution can affect volume of distribution (Vd)
  - A change in patient kidney or liver function affects drug clearance (CL)

- ***However*, these parameters do not directly interact with each other**
  - A change in volume of distribution does not change clearance and vice versa

Why is this distinction clinically important?

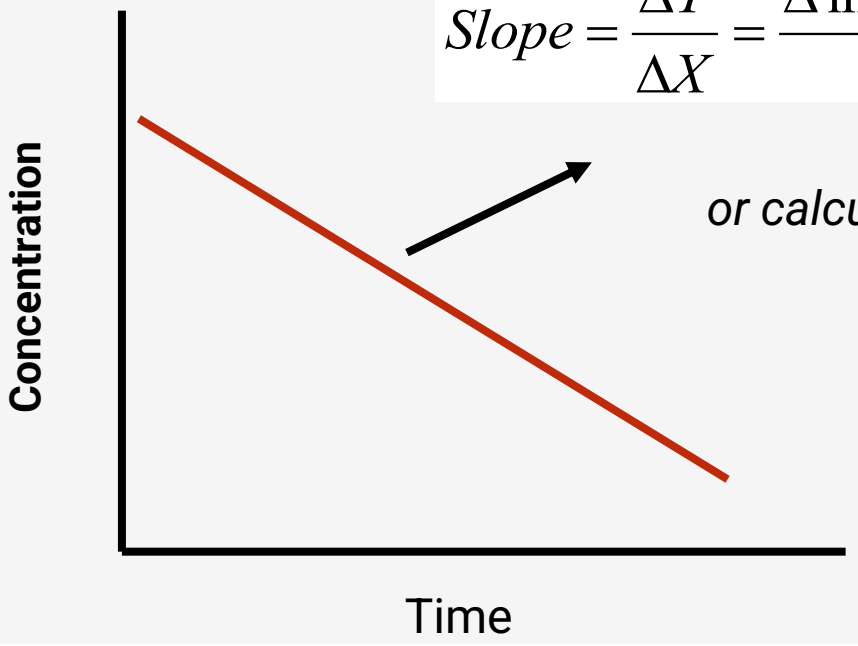
- **Volume of distribution**
  - Useful for calculating in *initial doses* of antibiotic regimens (loading dose)
- **Clearance**
  - Useful for calculating *maintenance doses* of antibiotic regimens
  - CL is NOT USED to determine how much of an initial dose (or loading dose) of an antibiotic to give to a patient

Key PK parameter #3- Elimination rate constant (k_{el})

What is k_{el}?

- Rate drug is removed per unit of time
- Calculated parameter: Unit of measure = reciprocal time (hr^{-1})

$$Slope = \frac{\Delta Y}{\Delta X} = \frac{\Delta \ln concentration}{\Delta time} = k_{el}$$



or calculated…

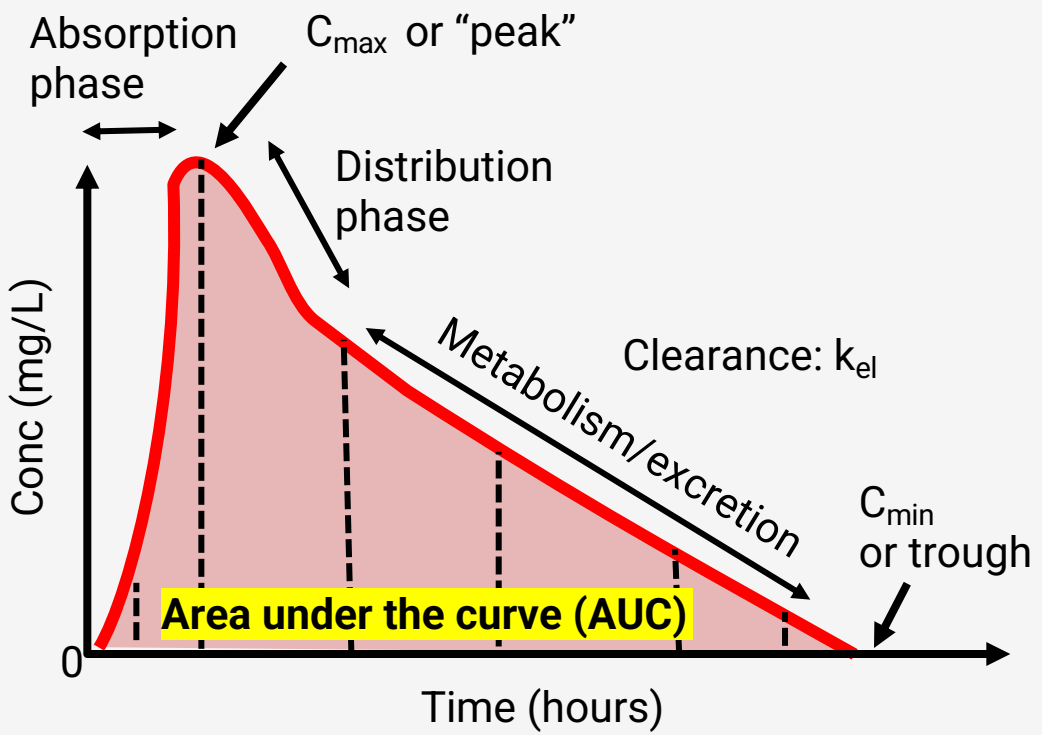
$$k_{el} = \frac{CL}{V_d}$$

Key PK parameter #4- Half-life

- **Time it takes for the plasma concentration or amount in the body to be reduced by 50%**
- **Calculated parameter**
  - Function of clearance and volume of distribution
    - Unit of measure = time (hours, minutes, days)

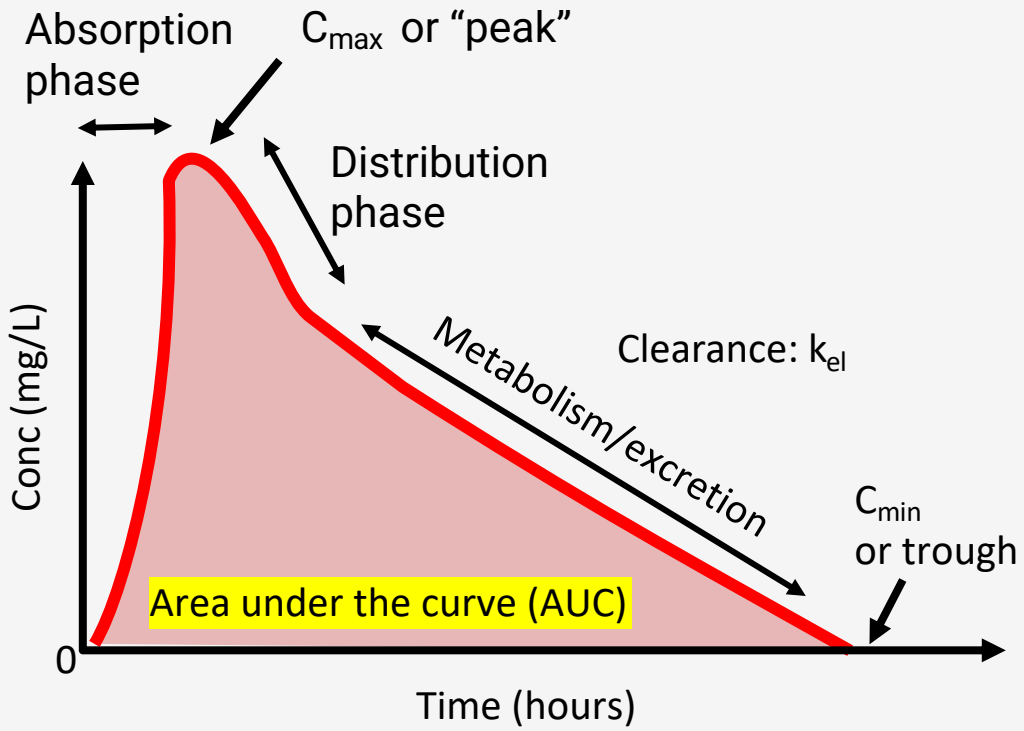
$$t_{1/2} = \frac{0.693 \times V_d}{CL} \qquad t_{1/2} = \frac{0.693}{k_{el}}$$

Key PK parameter #5- Area under the curve



- Total drug exposure over time, expressed as mg·h/L
- Dependent on the dose administered and rate of elimination
- Calculated by adding up or integrating the amounts of drug eliminated in discreet time intervals, from zero (time of the administration of the drug) to a defined time-e.g., 24 hours

Simplification of the AUC

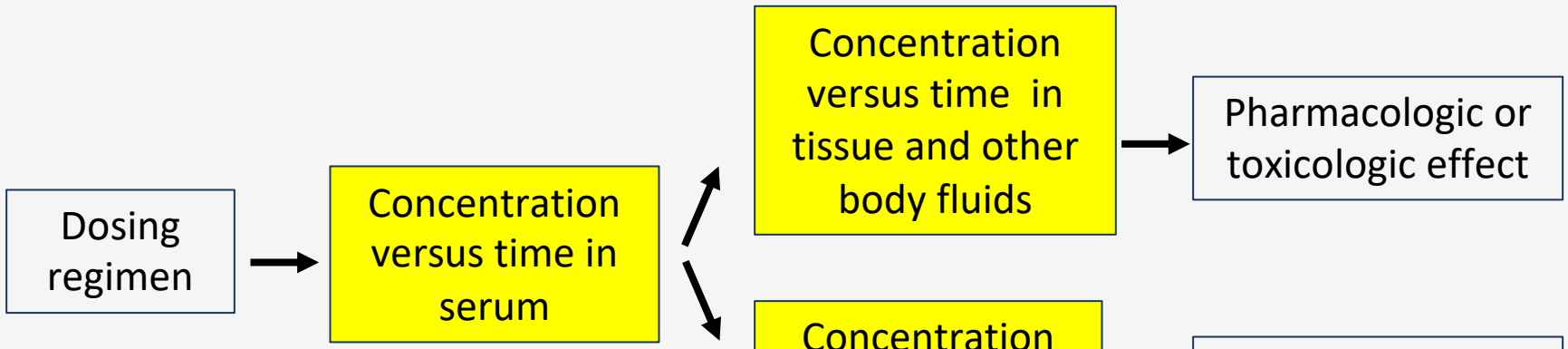


When expressed as for a given dosing interval (i.e. every 24 hours), we can simplistically consider it to represent average concentration

e.g., an antibiotic has an $AUC_{0\text{-}24h}$ 48 mg*h/L

$$\frac{48 \text{ mg} \cdot \text{hours/liter}}{24 \text{ hours}} = 2 \text{ mg/L average of 24 hours}$$

Pharmacology of antimicrobials



Absorption
Distribution
Metabolism
Elimination

Pharmacokinetics
"PK"

What the body does to drug

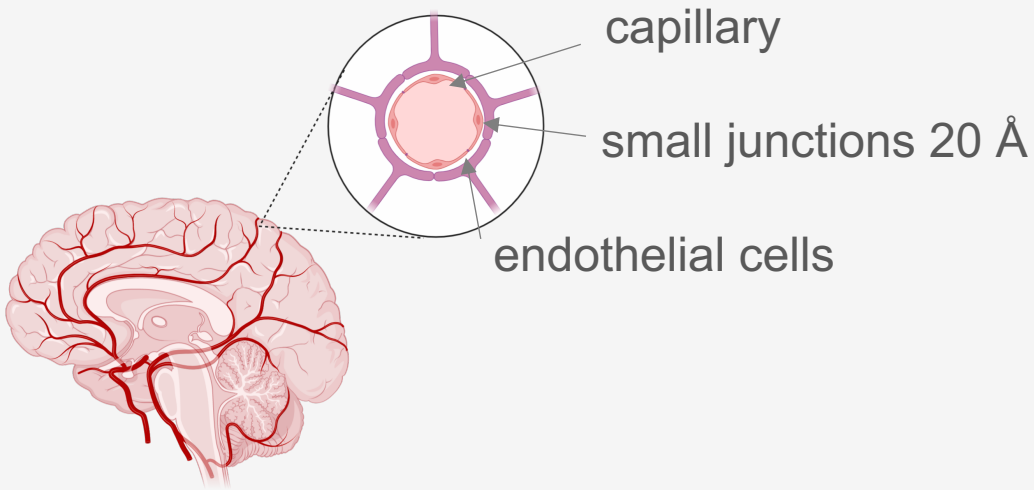
Pharmacodynamics
"PD"

What the drug does to the body (and bacteria)

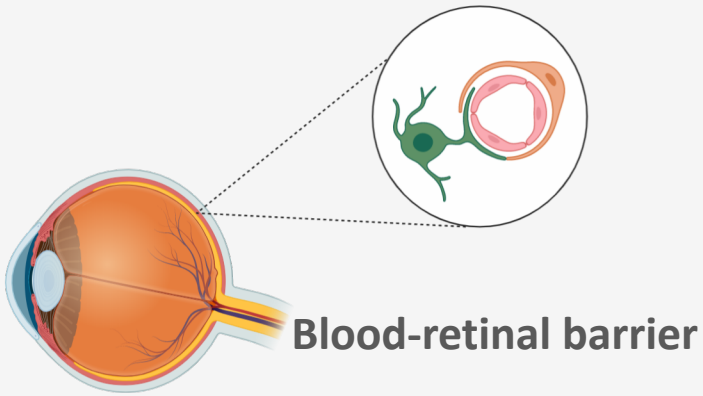
Craig WA. Clin Infect Dis 1998;26:1-12.

Antibiotic penetration at the site of infection

Anatomically-privlidged sites

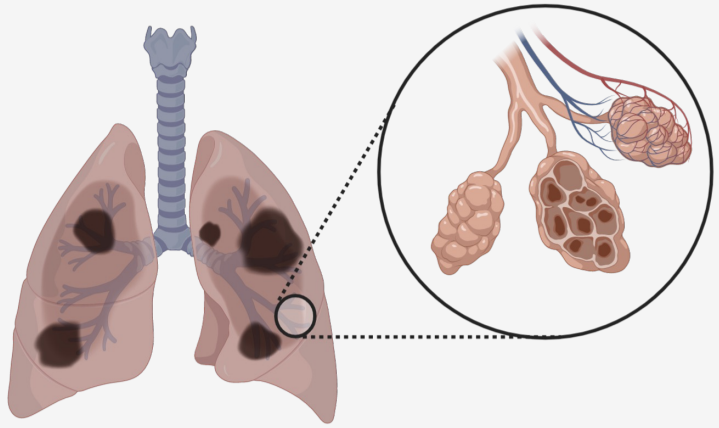


Blood-brain barrier



Blood-retinal barrier

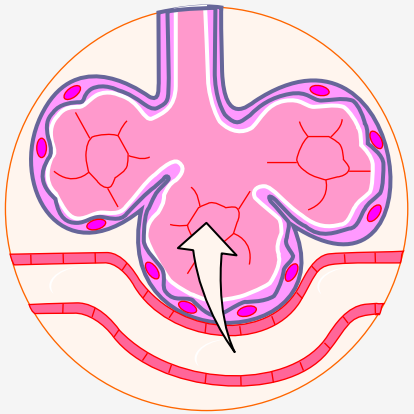
Inflammation, abscess, necrosis

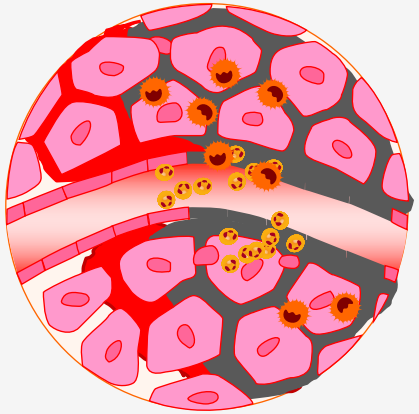


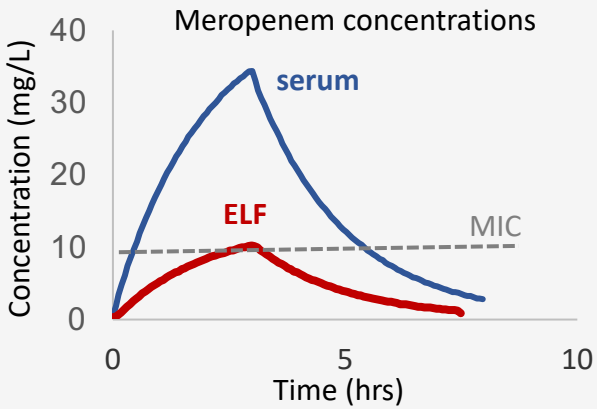
Antibiotic penetration influenced by:

- Serum drug concentrations
- Physiochemical properties of drugs
- Alterations in anatomic permeability (e.g., inflammation)
- Physiological barriers (e.g., blood-eye, blood brain barrier)
- Drug inactivation due to local pH, anaerobic conditions or enzyme activity

Antibiotic penetration-ventilator associated pneumonia





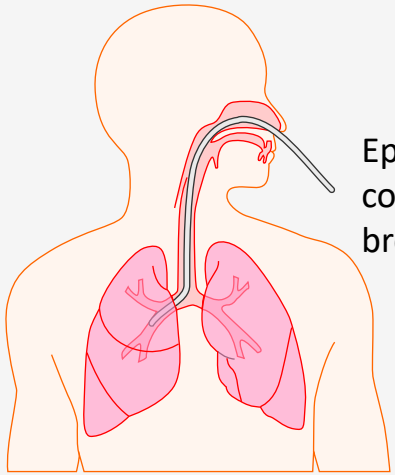


Antibiotic penetration through alveolar capillary barrier (*zona occludens*) by free, non-protein bound drug.

Must cross a transit area cleared by lymphatics

Enhanced by drug lipophilicity;

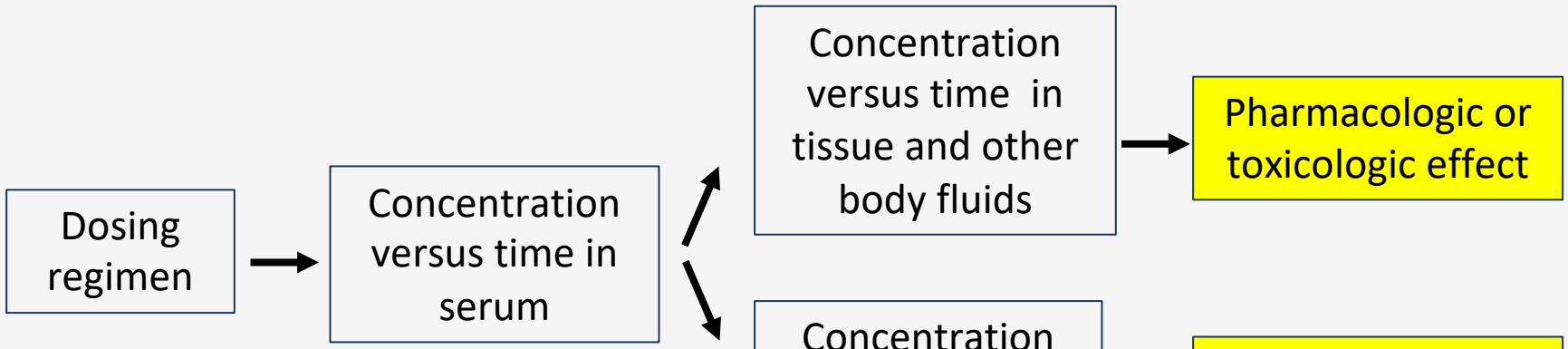
Penetration is reduced in infection, inflammation, necrosis, underlying lung disease, increased lymphatic clearance



Epithelial lining fluid (ELF) concentrations sampled by bronchoscopy

Lodise et al. Antimicrob Agent Chemother 2011;55:1606-1610.

Pharmacology of antimicrobials



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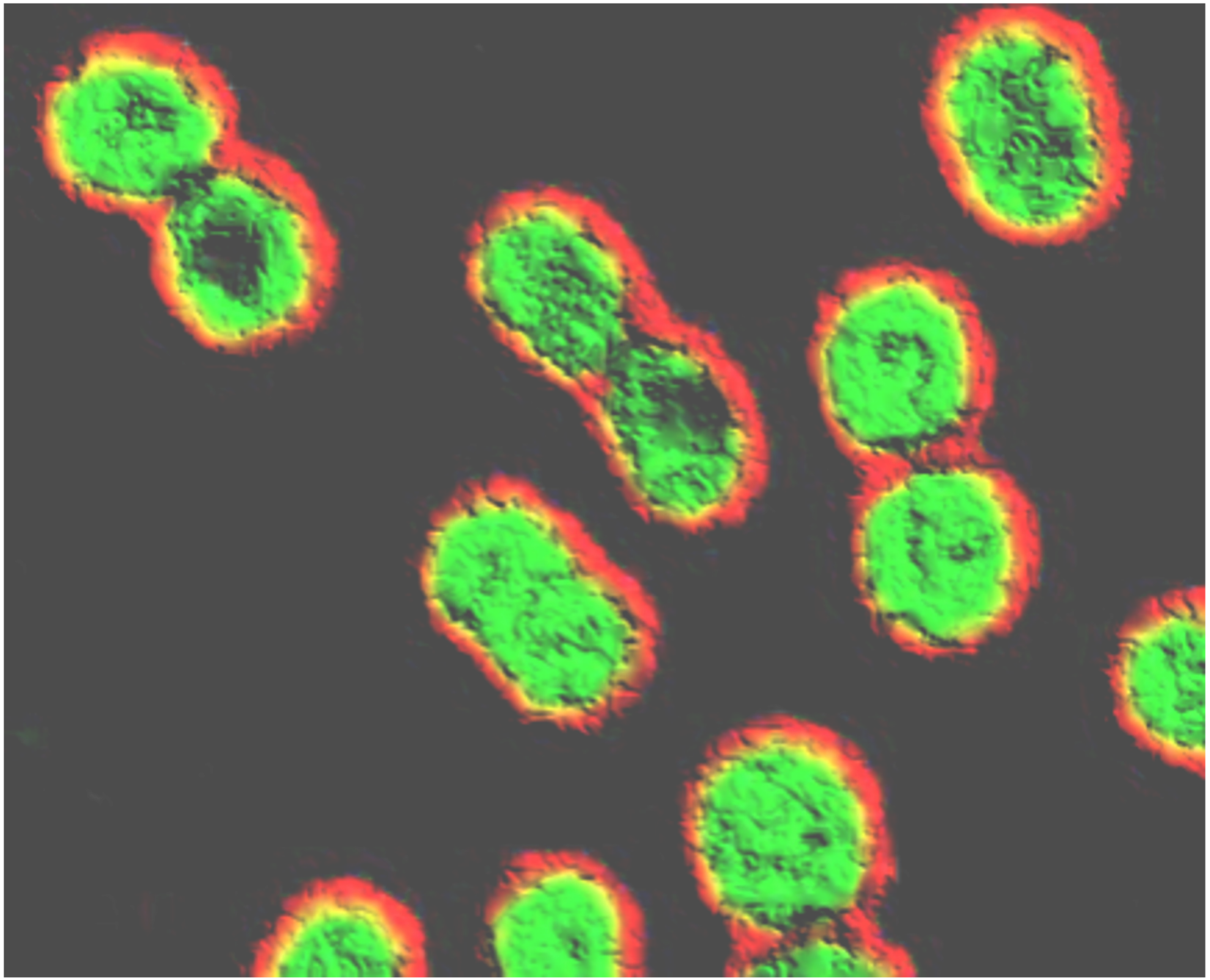
Laws of antimicrobial pharmacodynamics



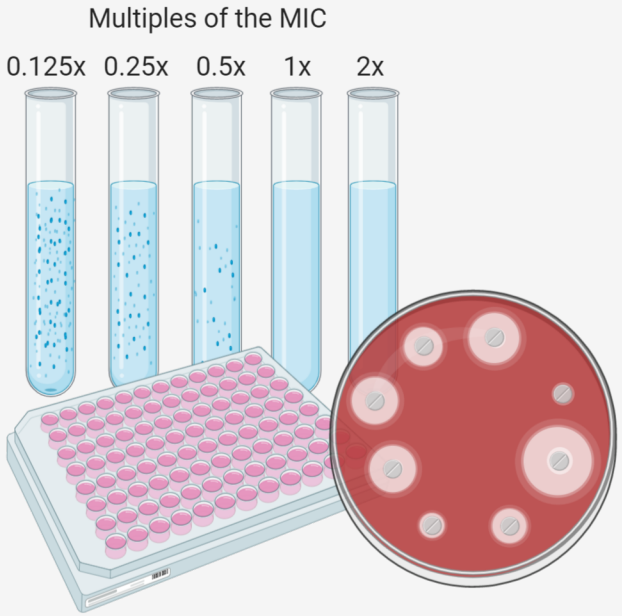
Laws of antimicrobial pharmacdynamics

- The shape of the antibiotic concentration versus antimicrobial effect curve is important for dosing

Drusano GL. *Nat Rev Microbiol* 2004;2:289-300.

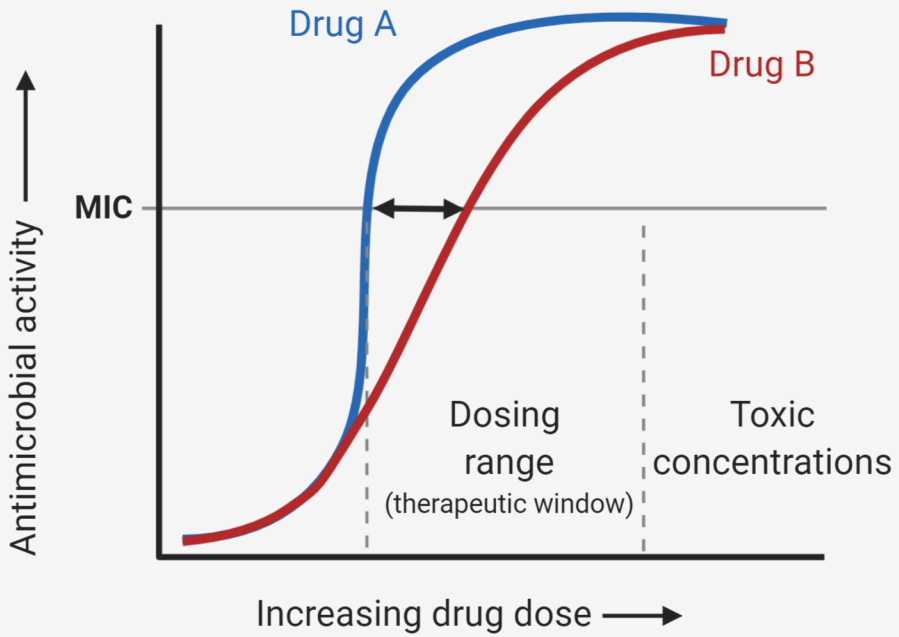
How does PD analysis differ from susceptibility testing?

Mean inhibitory concentrations (MIC)



- Good indicators of potency
- Tell us nothing about time course of antibiotic activity
- Nothing about dose-response relationship

Pharmacodynamics



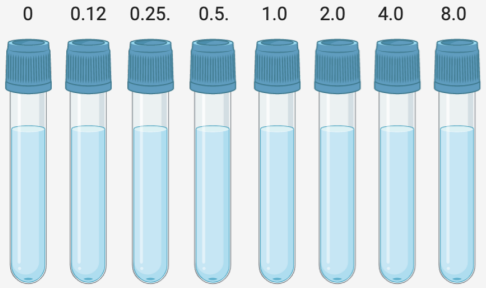
- How does the rate and extent of bacterial killing by an antibiotic change at concentrations near and above the MIC?
- The shape of the curve affects drug dosing strategies

Craig WA. Clin Infect Dis 1998;26:1-12.

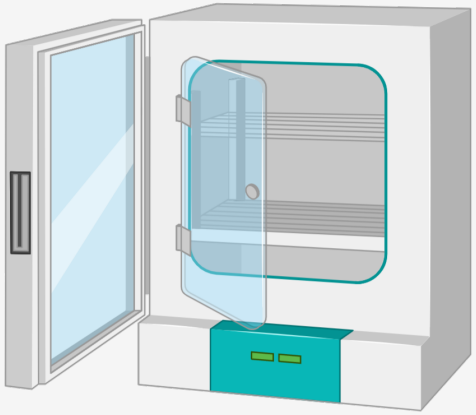
How to define the shape of the concentration-effect curve

Standardized inoculum of bacteria in each tube + Serial dilutions (multiples of MIC) of antibiotic

Multiples of MIC



Incubate for 24h at 35°C



Sample tubes at 0, 0.5, 1,2,4,8, 12 and 24 hours

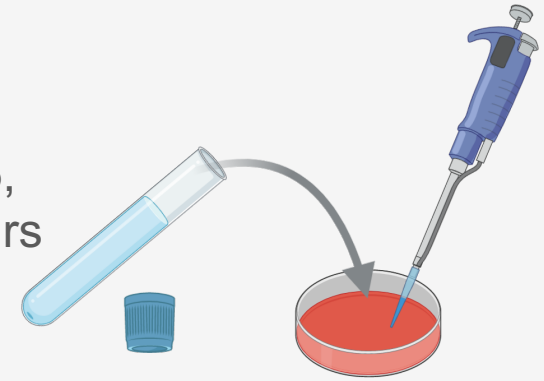
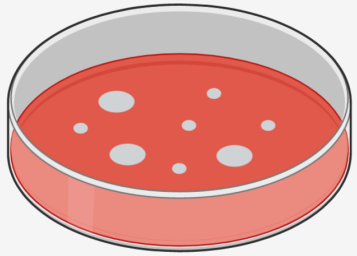


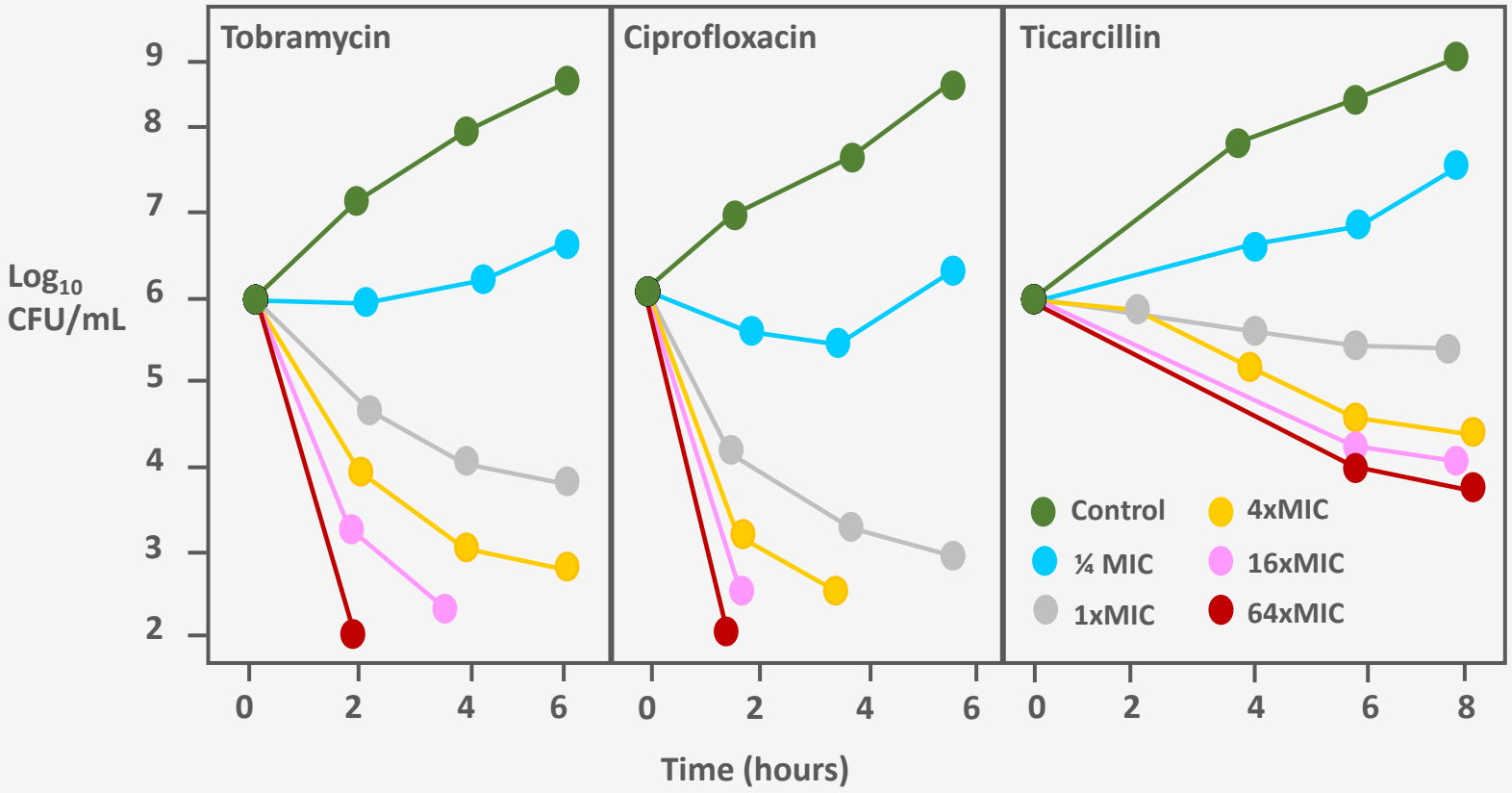
Plate of microbiological agar, incubate for 24 hours

incubate



Count number of viable colony forming units (CFU) on each plate

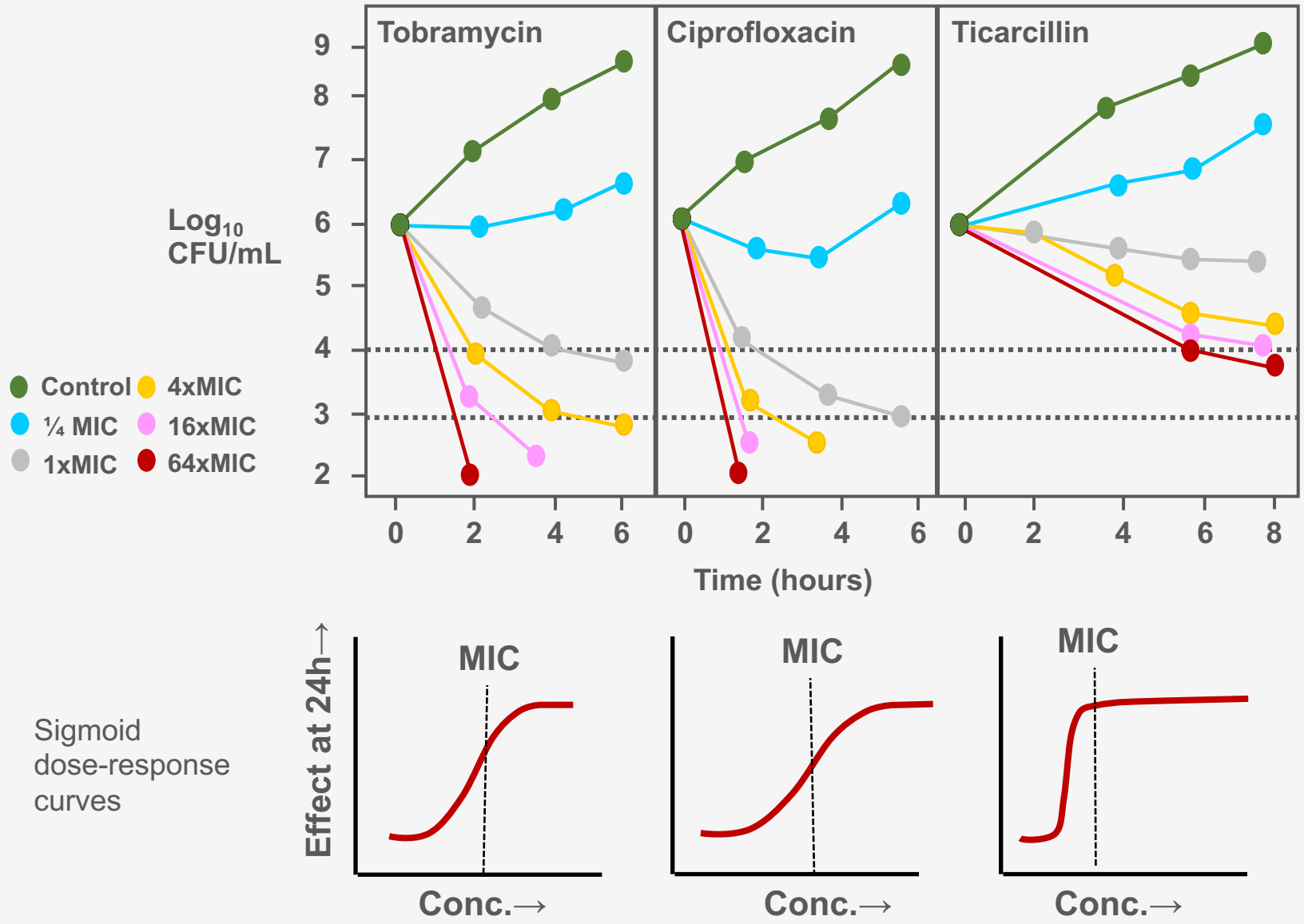
In vitro antibiotic time-kill curves



Key questions:

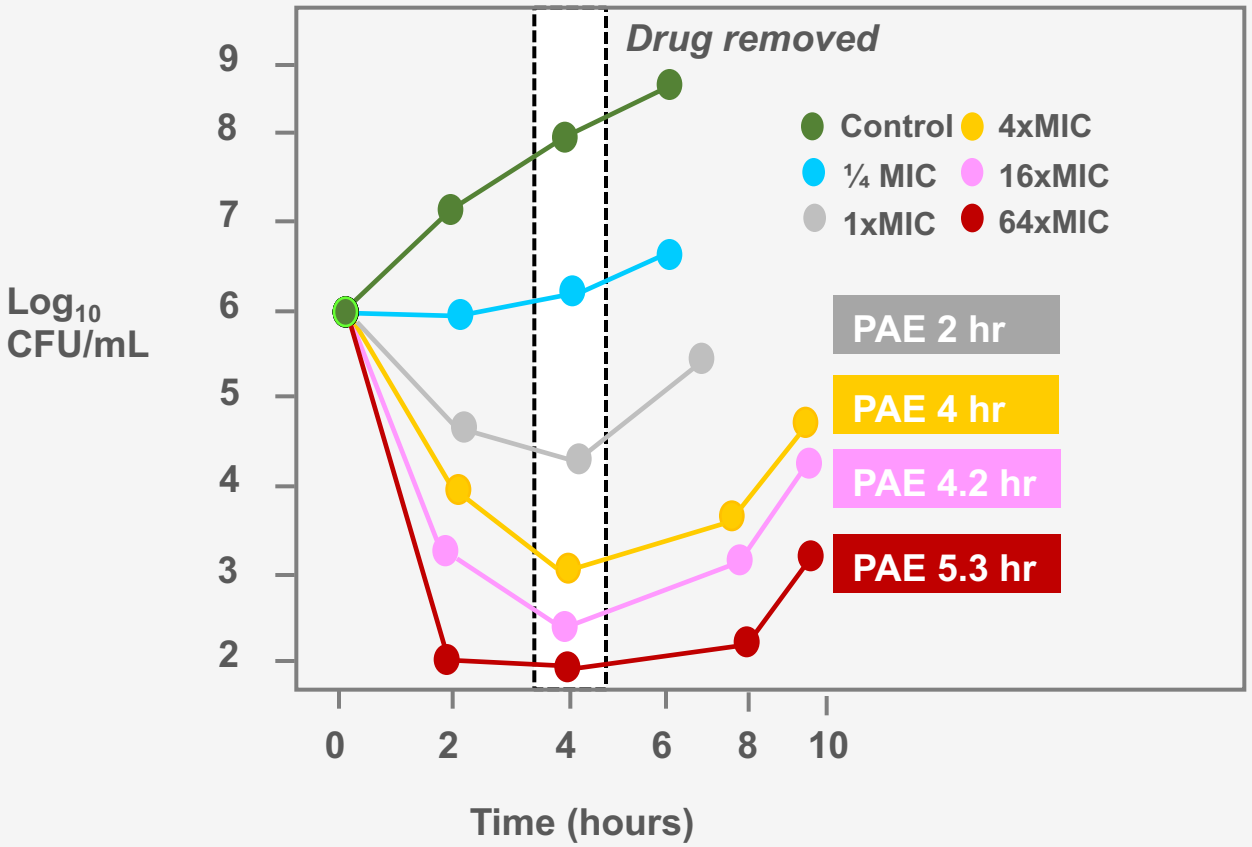
- Did the rate and extent of killing increase at higher MIC multiples?
- What is the multiple of MIC where killing was maximized?
- Did the antibiotic achieve bacteriostatic (2-$\log_{10}$) or bactericidal (3-$\log_{10}$) reductions in CFU?

Craig WA et al. *Scand J Infect Dis* 1991;74:63-70.


Tobramycin
Ciprofloxacin
Ticarcillin
Log10 CFU/mL
9
8
7
6
5
4
3
2
0
2
4
6
8
Time (hours)
Control
¼ MIC
1xMIC
4xMIC
16xMIC
64xMIC
Sigmoid dose-response curves
Effect at 24h→
MIC
Conc.→

Post-antibiotic effect (PAE)

Persistent antibiotic effect after drug removal



Generally reported as time to 1-$\log_{10}$ increase after drug removal

Craig WA et al. *Scand J Infect Dis* 1991;74:63-70.

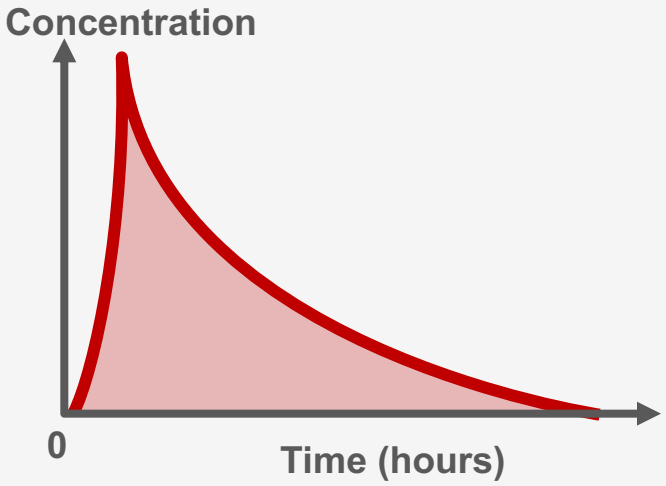
How do you translate these results to patients?

In vitro

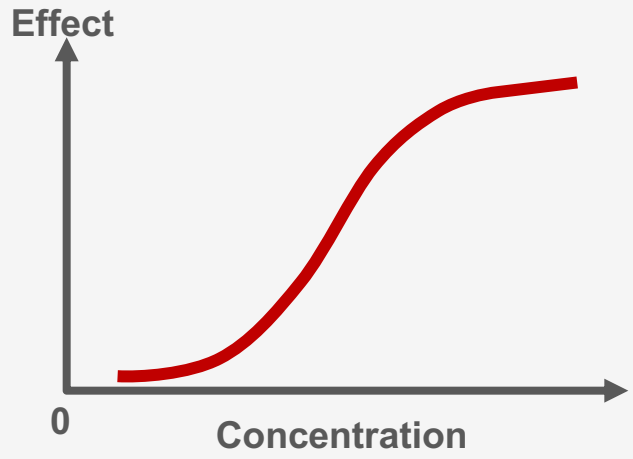
In vivo
(animal model)

Patients

Pharmacokinetics (PK)
concentration vs. time

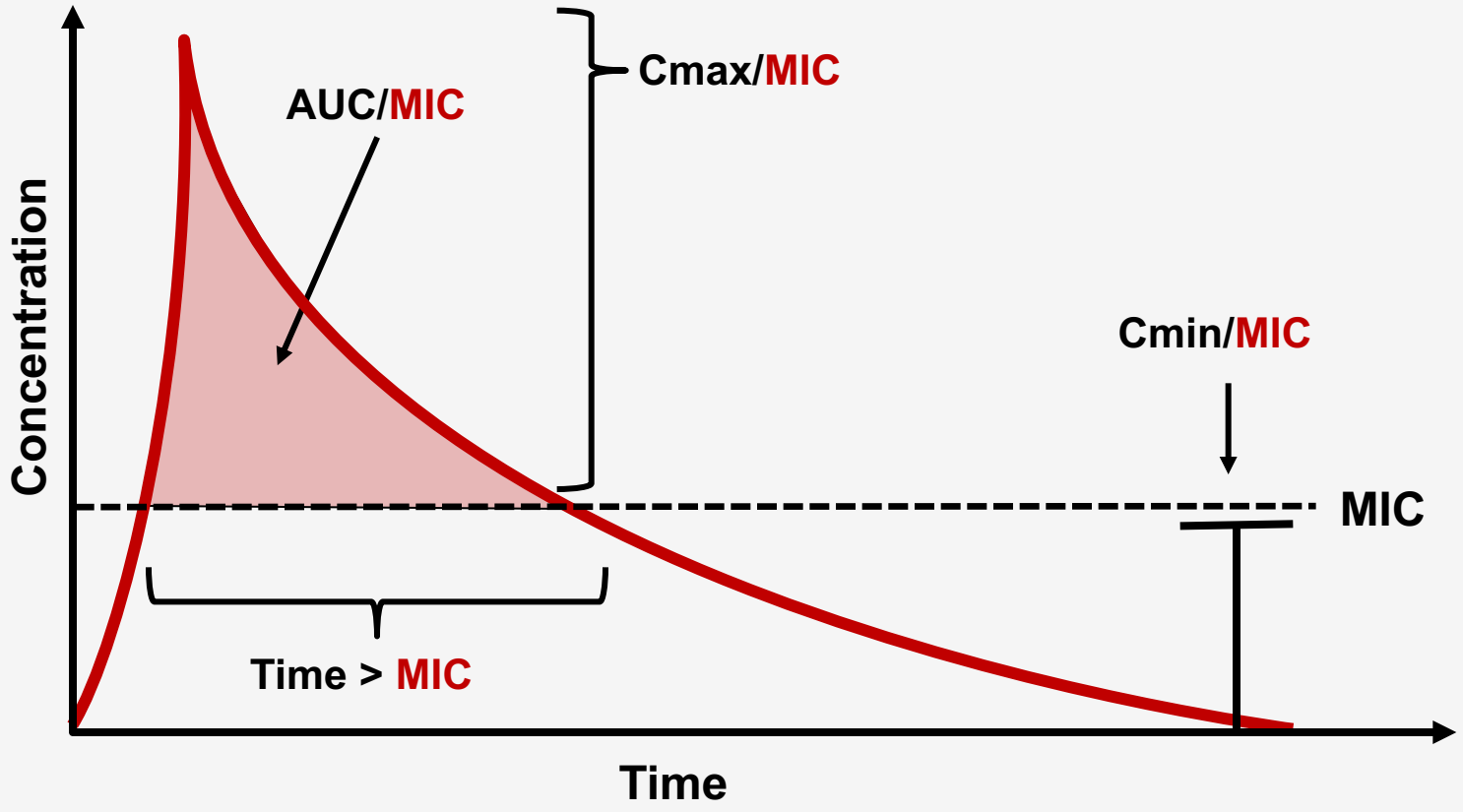


Pharmacodynamics (PD)
concentration vs. effect



PK:PD
effect vs. time

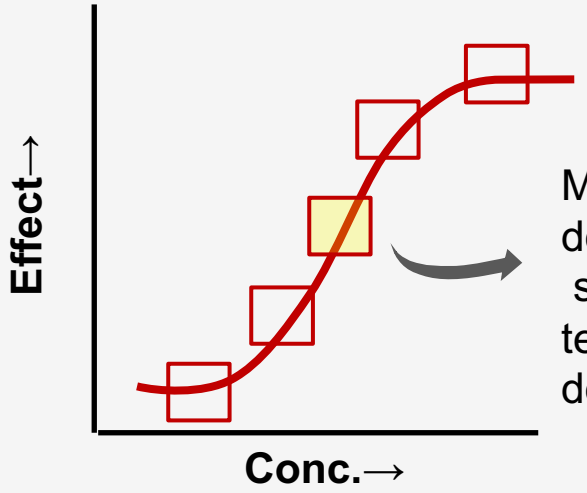
Common PK/PD Indices



AUC = Area under the concentration–time curve; MIC = Minimum Inhibitory Concentration; C_{max} = Maximum or peak plasma concentration; C_{min} = Minimum or trough plasma concentration

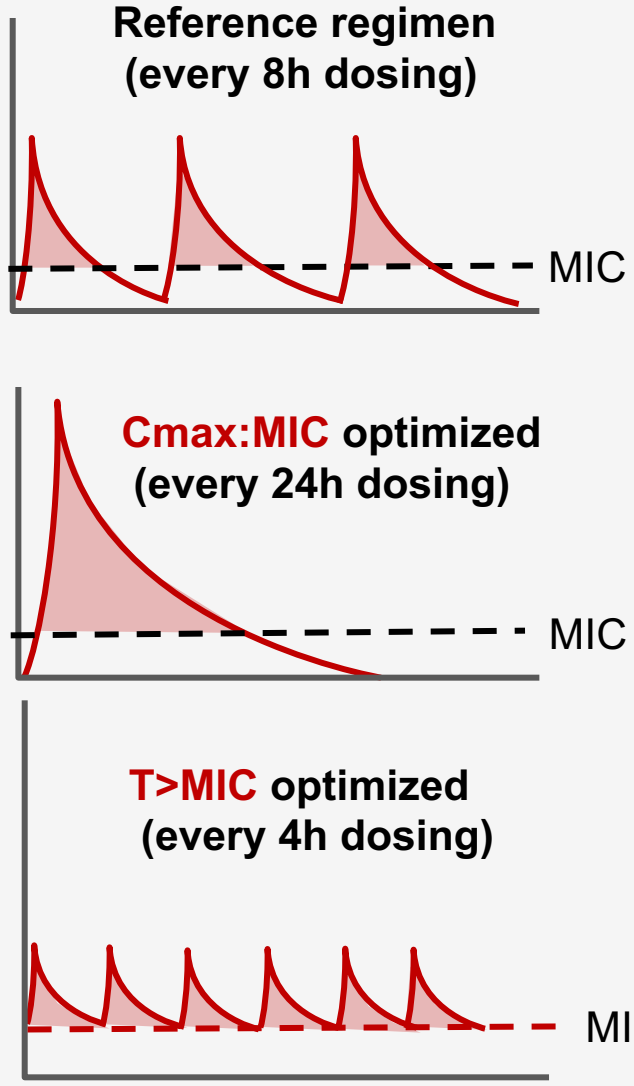
Dose fractionization study

Test a range of doses to define (or confirm) shape of dose-response curve

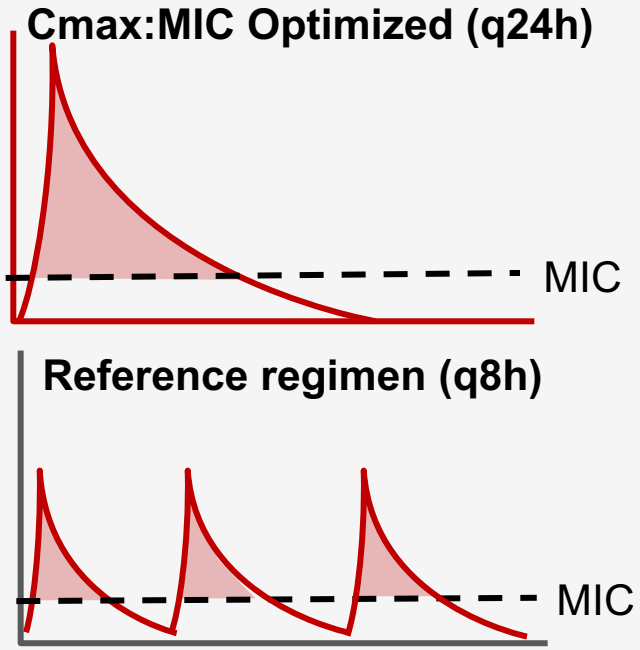


Moderately effective dose (AUC exposure) selected for further testing at different dose intervals

All dosing regimens have the same AUC



Dose fractionization study interpretation



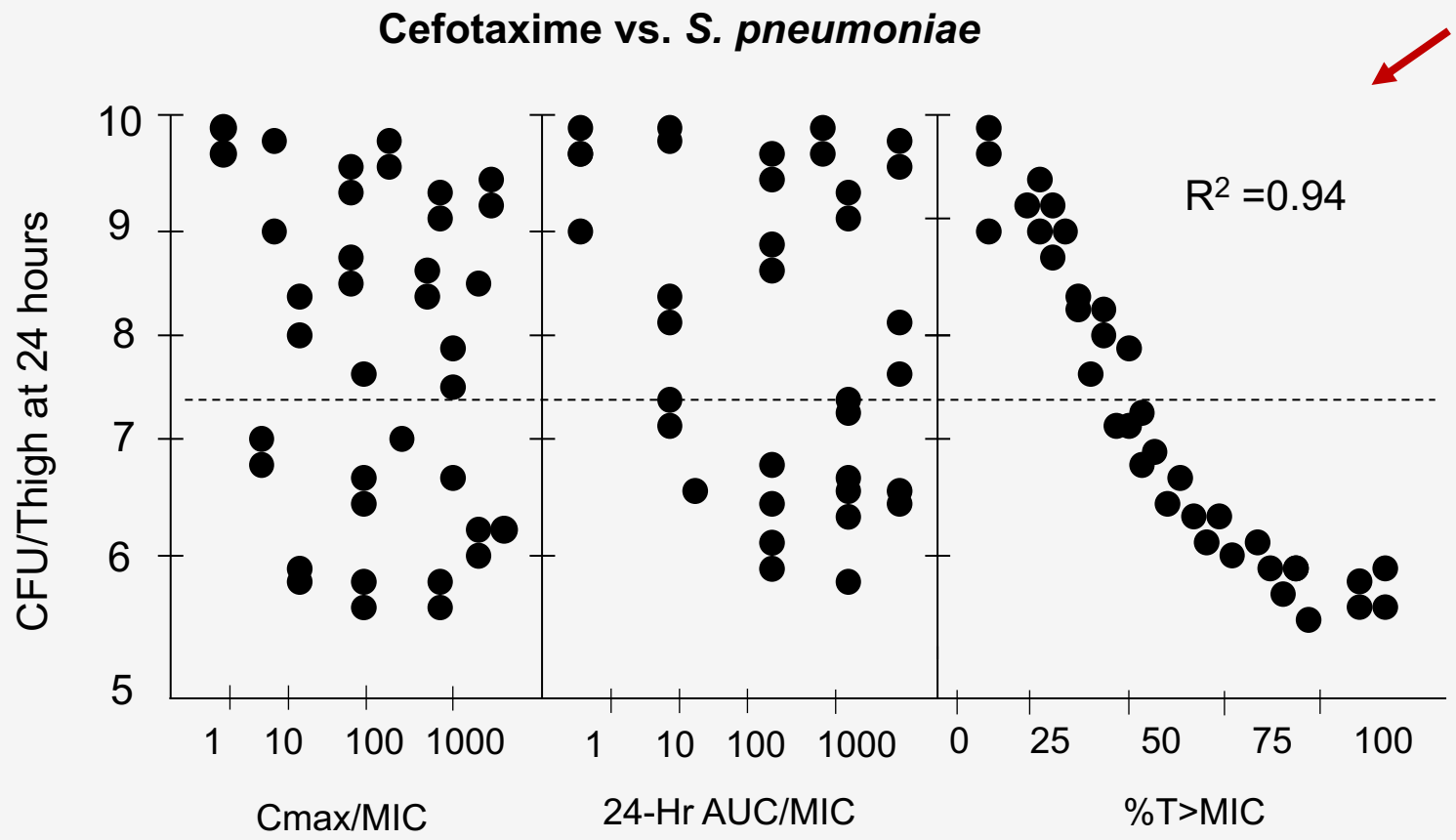
Efficacy Observation	Dosing parameter important to optimize
q24h > q8h > q4h	Cmax/MIC
q24h = q8h =q4h	AUC/MIC
q24h < q8h< q4h	%time >MIC

These experiments tell us what component of the dosing strategy drives antibiotic effect

Example of dose-fractionization study results

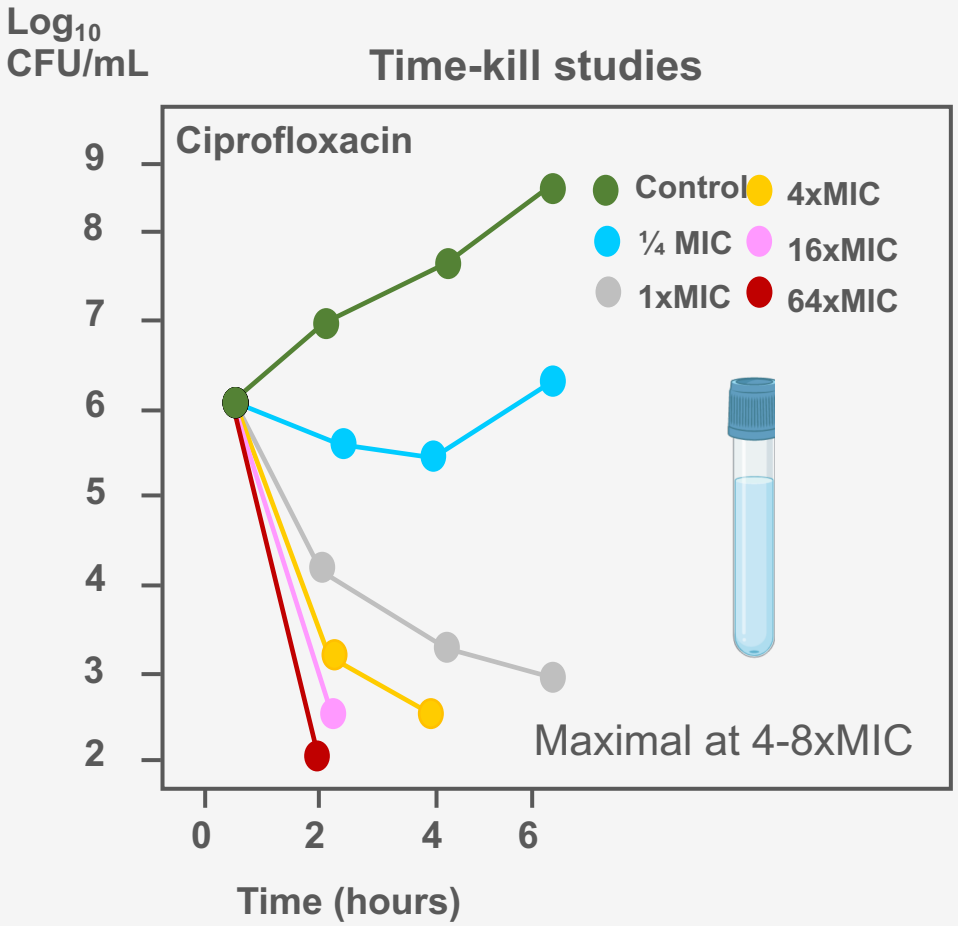
Neutropenic murine thigh infection model;
Dose-fractionated study

Activity best correlates with %T>MIC



Craig WA. *Diagn Microbiol Infect Dis* 1995: 22:89-96

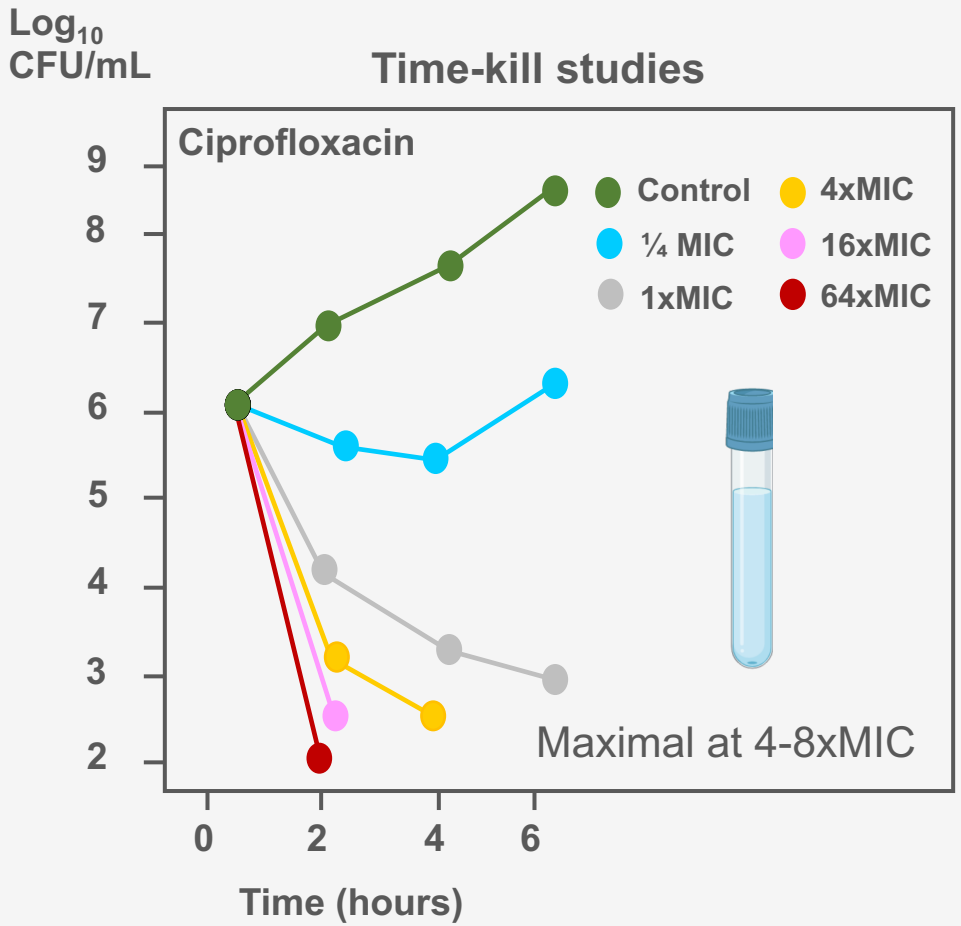
Example of in vitro/in vivo PK/PD correlation

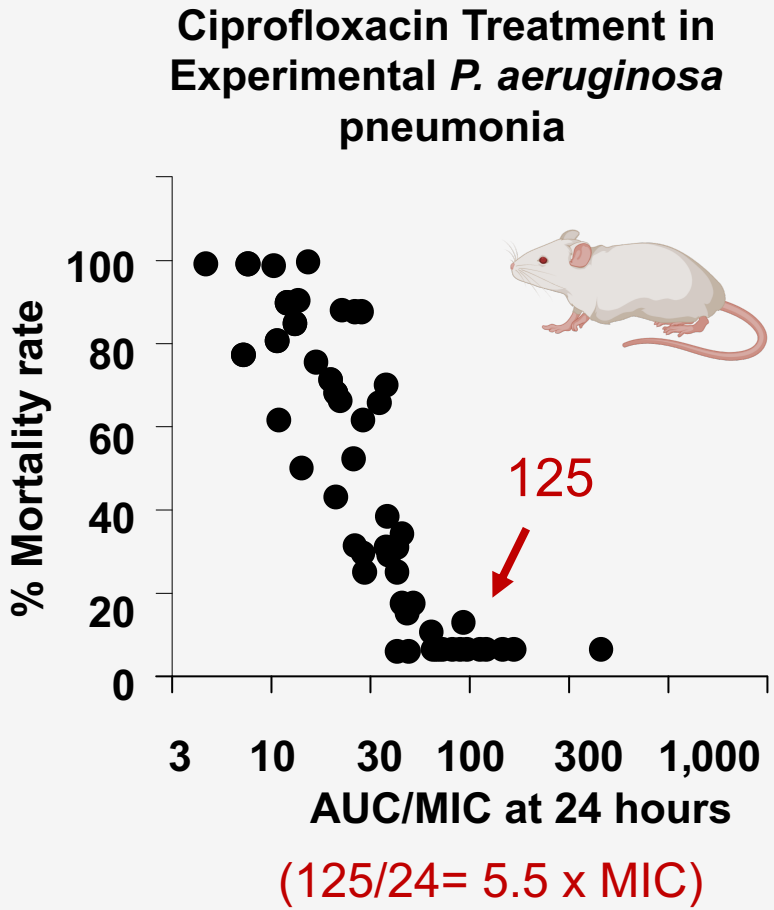


- Remember and $AUC_{0\text{-}24h}$ is approximately equivalent to the average concentration over 24 hours
- So if we see maximal killing at 4-8xMIC in the test tube, We might predict that an AUC/MIC of 96-196 in animals would be associated with maximal ciprofloxacin efficacy

Craig WA. *Infect Dis Clin N Amer* 2003;17:479

Example of in vitro/in vivo PK/PD correlation

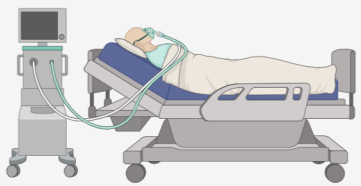


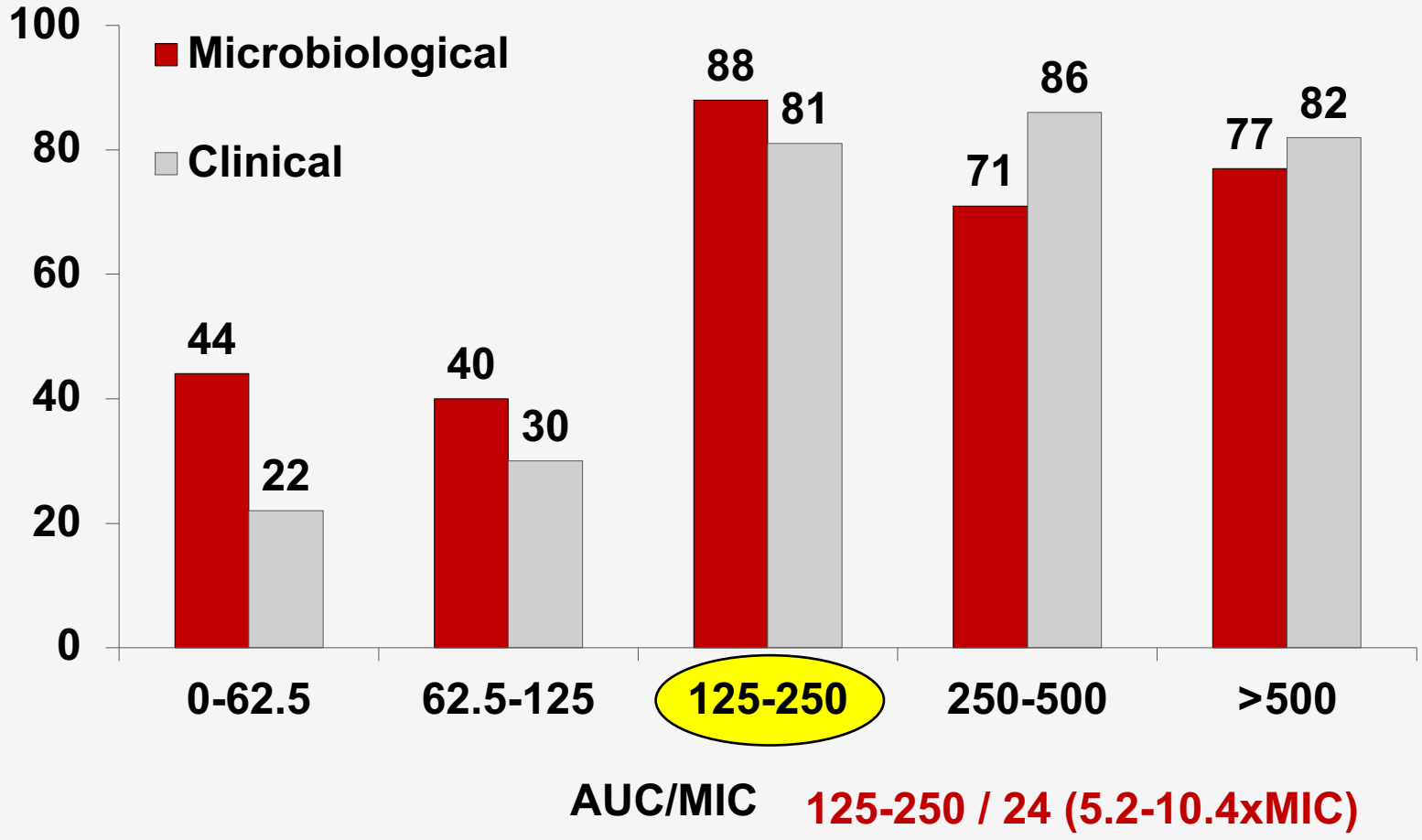


(125/24= 5.5 x MIC)

Craig WA. *Infect Dis Clin N Amer* 2003;17:479

Ciprofloxacin for nosocomial pneumonia:
Correlation between drug exposure and clinical outcome





Forrest A et al. *Antimicrob Agents Chemother* 1993;37:1073-81.

Pharmacodynamic parameters predictive of outcomes in animals and humans

	C_{max}/MIC	AUC/MIC	T>MIC
Examples	Aminoglycosides Fluoroquinolones Polymyxins **Also predicted by AUC:MIC**	Azithromycin Fluoroquinolones Ketolides Linezolid Daptomycin Vancomycin Tigecycline	Penicillins Cephalosporins Carbapenems Monobactams Macrolides
Organism kill	Concentration-dependent	Concentration and time dependent	Time-dependent
Dosing goal	Maximize exposure	Maximize exposure	Optimize duration of exposure

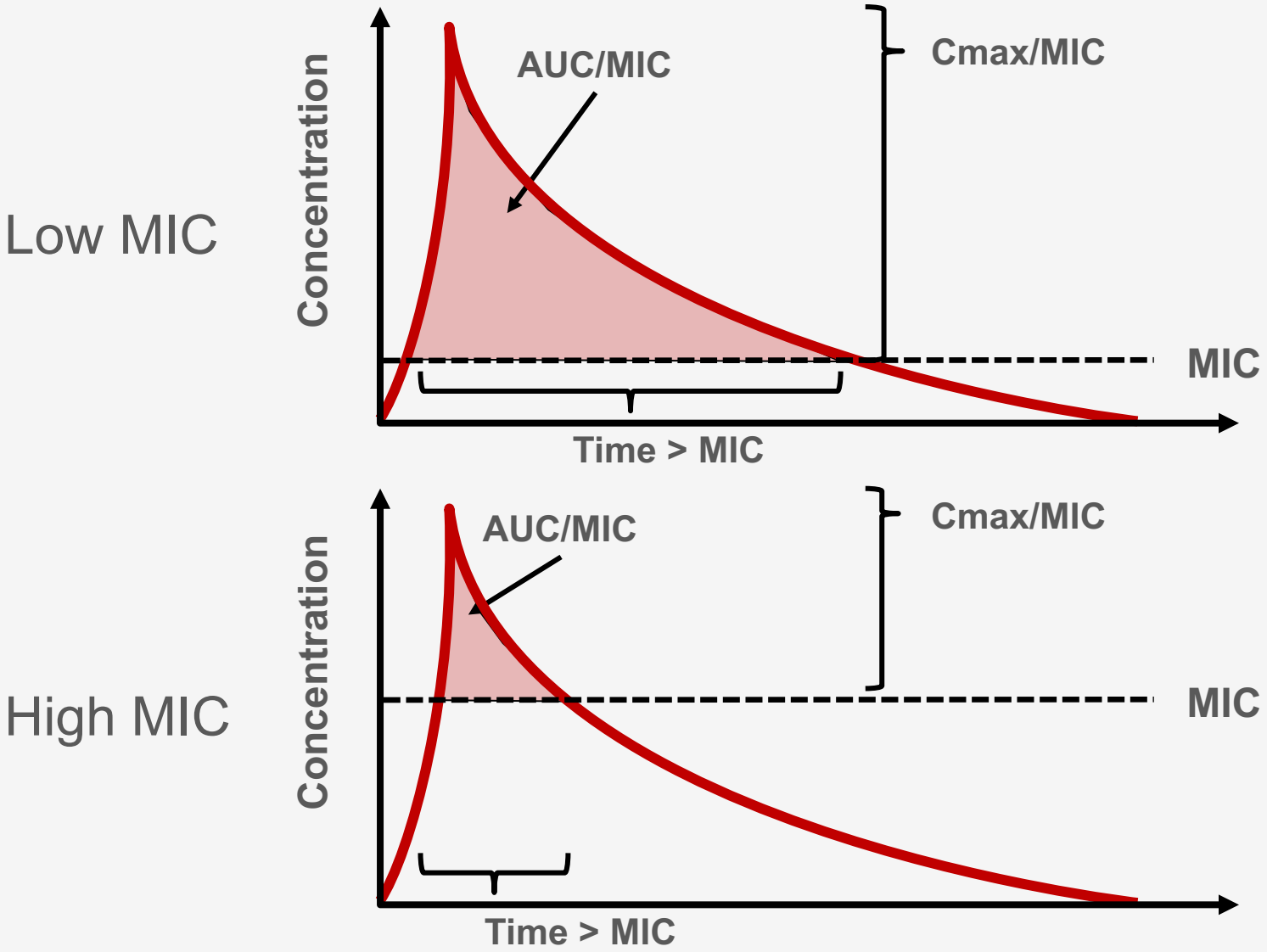
Drusano & Craig. *J Chemother* 1997;9:38–44 ; Drusano et al. *Clin Microbiol Infect* 1998;4 (Suppl. 2):S27–S41,

Laws of antimicrobial pharmacdynamics

- The shape of the antibiotic concentration versus antimicrobial effect curve is important for dosing
- Only free-drug (non-protein bound fraction) is microbiologically active
- A higher MIC will diminish the effect of a fixed dose

Drusano GL. *Nat Rev Microbiol* 2004;2:289-300.

Effect of increasing MIC



Laws of antimicrobial pharmacodynamics

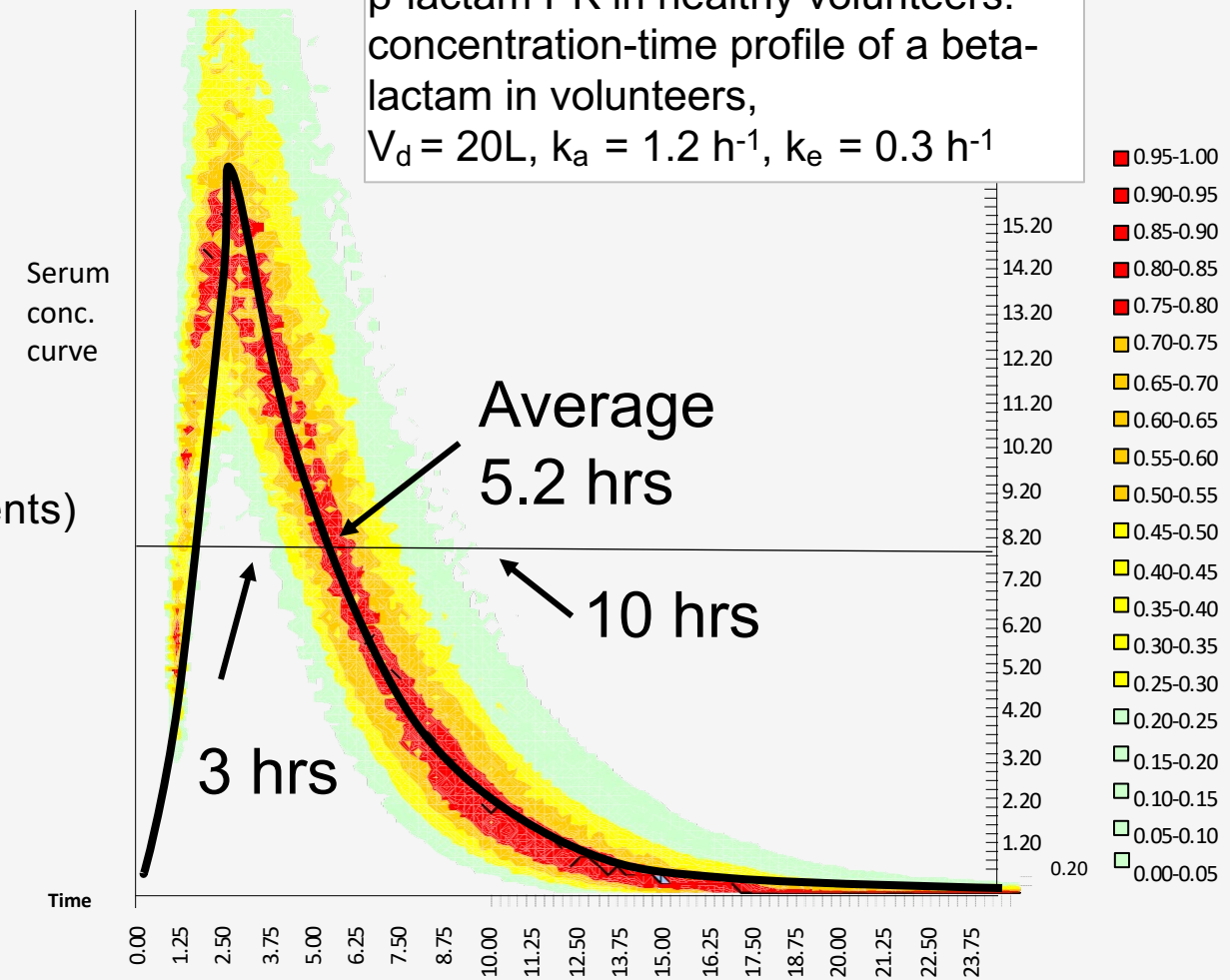
- The shape of the antibiotic concentration versus antimicrobial effect curve is important for dosing
- Only free-drug (non-protein bound fraction) is microbiologically active
- A higher MIC will diminish the effect of a fixed dose
- Administering a fixed dose of drug to many patients (even on a mg/kg basis) results in wide variability in exposure

Drusano GL. *Nat Rev Microbiol* 2004;2:289-300.

Pharmacokinetics vary from one patient to the next

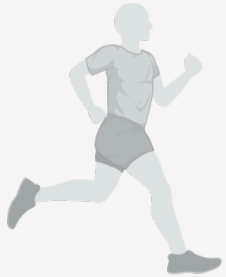
β-lactam PK in healthy volunteers: concentration-time profile of a beta-lactam in volunteers,
V_d = 20L, k_a = 1.2 h^{-1}, k_e = 0.3 h^{-1}

Simulation (5,000 patients) probability at 20% CV



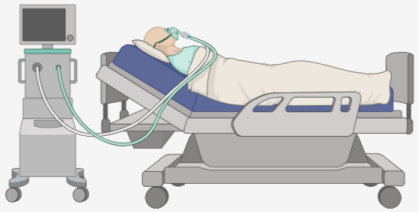
Mouton J. Inter J Antimicrob Agent 2012

Which patients are studied in clinical trials?



Healthy volunteers (Phase I studies; 10-20% CV in PK parameters)

Patients with non-life threatening infections, e.g., skin and soft tissue infection, urinary tract infection (phase II/II studies; normally 15-30% CV in PK parameters)



Critically-ill ICU patients (phase IV; 80-200% CV in PK parameters)

CV-Coefficient of variation
(variability in relation to population mean)

Drusano et al. Antimicrob Agent Chemother 2011;55:3406-3412.

Factors reducing antibiotic clearance

- **Renal function impairment**
  - Cockcroft-Gault formula (other formulas MDRD…etc.)

$$CrCl_{estimated} = \frac{(140 - age)\,x\,weight(kg)}{72x(Serum\ creatinine)}\,x0.85(if\ female)$$

  - Use ideal body weight if actual body weight > 20% higher than IBW, or if patient has severe edema/ascites
  - Overestimates renal function in patients with low body weight /muscle mass
  - Less accurate in patients with fluctuating renal function
  - Dialysis (drug-specific dosing guidance)
- **Liver dysfunction**
  - Only very general dosing recommendations (i.e. based on Child-Pugh scores)

Be careful about prematurely reducing antibiotic doses in patients with acute renal impairment!

- Antibiotic renal dose adjustments in drug labeling are based on patients with *chronic kidney disease*
- Renal impairment is acute, not chronic, in up to 50% of patients with infection and frequently resolves within the first 48 hours
- Creatine-based equations for estimates of CrCl are based on steady-state conditions, and not as accurate in acute kidney injury
  - Decreases in SeCr are delayed with respect to injury resolution
- **Renal dose reduction in the first 48 hours of therapy may unnecessarily result in underdosing of antibiotics, especially for "safe" antibiotics**

Crass RL et al. Clin Infect Dis 2019; 68:1596–1602.

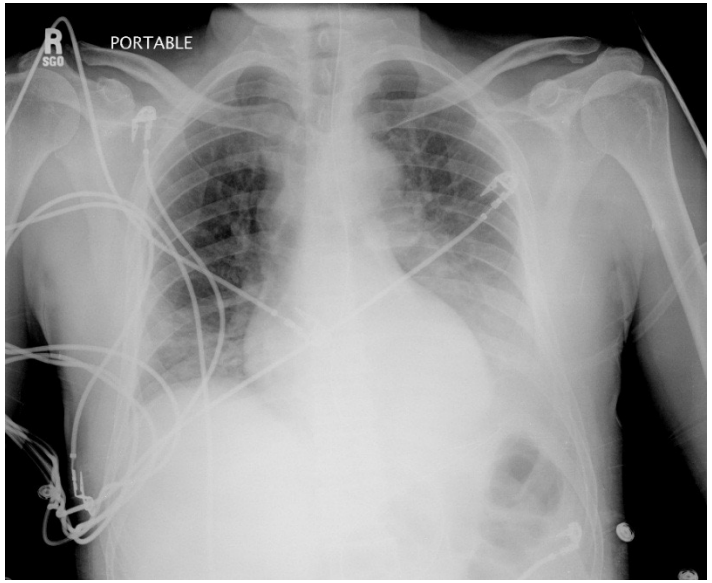
Augmented renal clearance (CrCL> 130 mL/min)

- **Common causes:**
  - "hyperdynamic state" with Gram-negative sepsis, vasoactive medications to support blood pressure
  - large-volume fluid resuscitation
- **Most common populations with augmented clearance**:
  - younger patients (i.e. trauma)
  - Severe burn patients
  - pregnant patients
  - septic patients without renal dysfunction
- **Often leads to *inadequate* antibiotic exposures**

Udy et al. Chest 2012;142:30-39.

Patient Case #1

- You have a 45-year-old patient in the ICU with suspected ventilator-associated on pneumonia. He is currently receiving piperacillin-tazobactam 3.75 gram every 6 hours. You are asked by the unit director to write new antibiotic orders for meropenem + gentamicin
  - Bronchial aspirate culture: *Pseudomonas aerugionsa*
  - Meropenem MIC= 1 mcg/mL (S)
  - Gentamicin MIC=1 mcg/mL (S)



Patient case cont.

- The patient weighs 70 kg, 180 cm, SeCr 0.9 mg/dL
- You use the Cockcroft-Gault formula to calculate that the patient has an estimated GFR ($CrCL_{est}$) of 103 mL/min

$$\frac{(140 - 45\,years)x70kg}{72\,x\,0.9\,mg\,/\,dL} = 103\,mL\,/\,\min$$

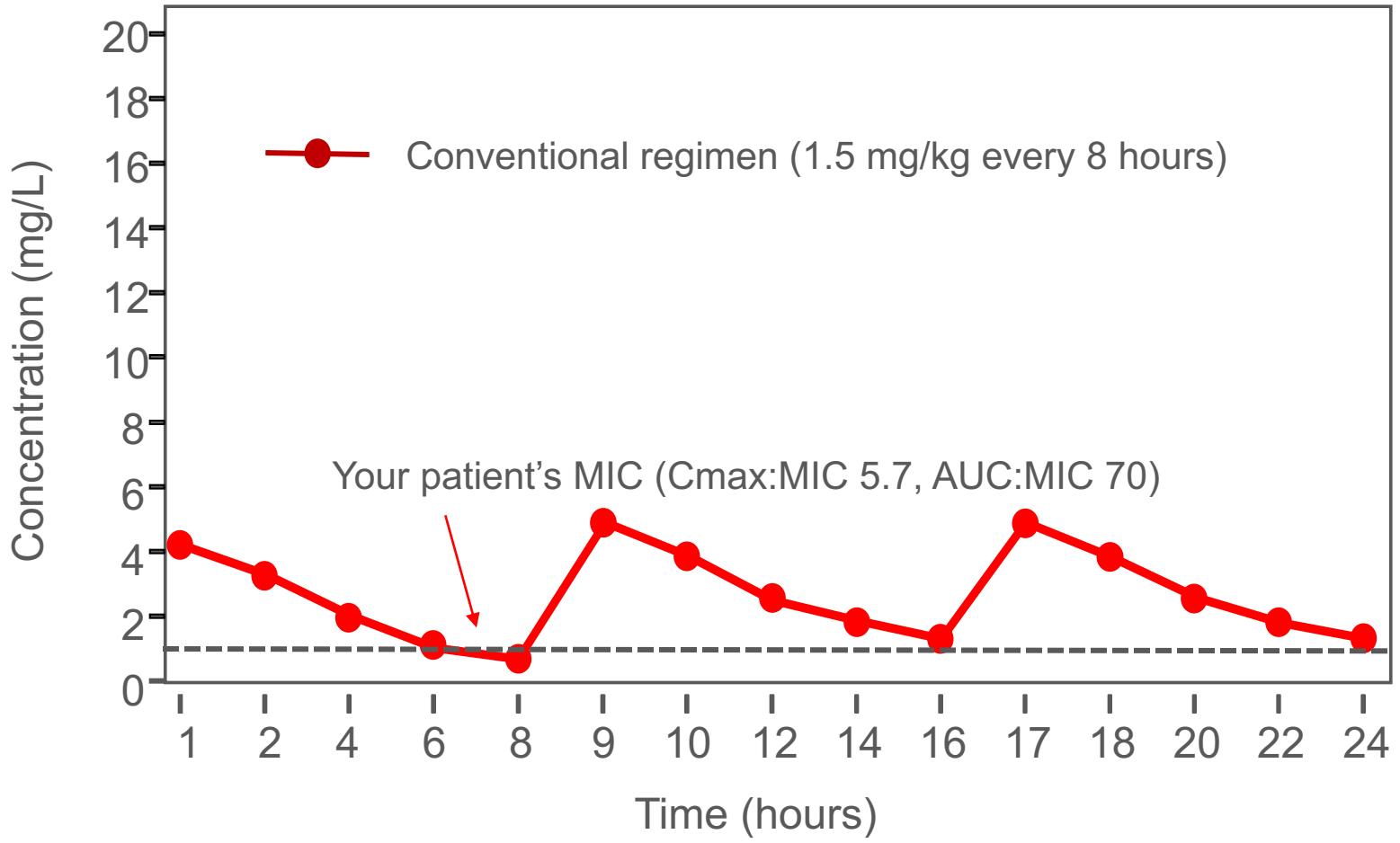
- Based on the drug reference on your cellphone, you see the standard doses are:
  - Meropenem 1 gram every 8 hours *adjusted for renal function*
  - Gentamicin 1.5 mg/kg every 8 hours *adjusted for renal function*

Pharmacodynamic parameters predictive of outcomes in animals and humans

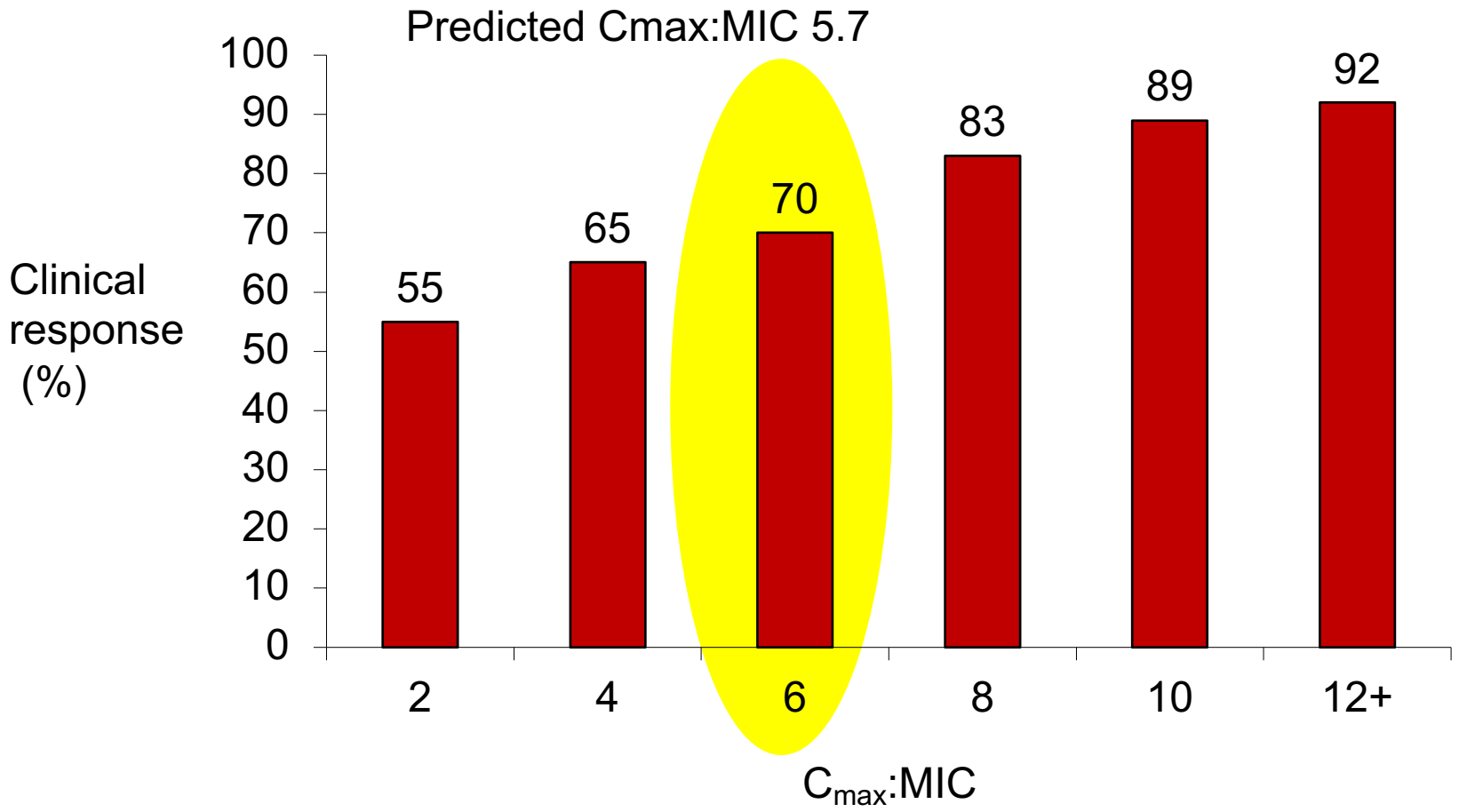
	C_{max}/MIC	AUC/MIC	T>MIC
Examples	Aminoglycosides Fluoroquinolones Polymyxins **Also predicted by AUC:MIC**	Azithromycin Fluoroquinolones Ketolides Linezolid Daptomycin Vancomycin Tigecycline	Penicillins Cephalosporins Carbapenems Monobactams Macrolides
Organism kill	Concentration-dependent	Concentration and time dependent	Time-dependent
Dosing goal	Maximize exposure	Maximize exposure	Optimize duration of exposure

Drusano & Craig. *J Chemother* 1997;9:38–44 ; Drusano et al. *Clin Microbiol Infect* 1998;4 (Suppl. 2):S27–S41,

Your Patient's Predicted Gentamicin Regimen

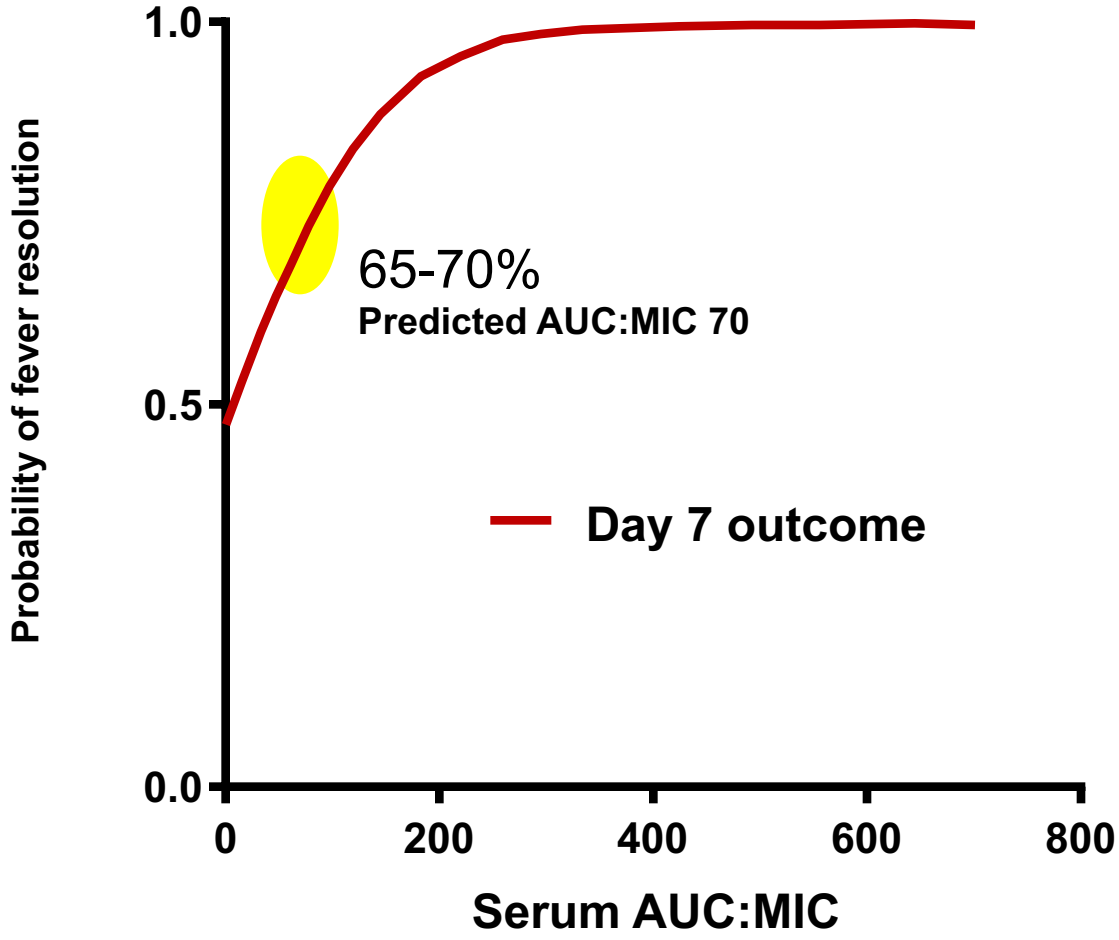


Aminoglycosides:
Relationship between C_{max}/MIC ratio and clinical response in patients



Moore RD et al. *J Infect Dis.* 1987;155:93-9.

Relationship of gentamicin exposures and treatment response (multiple daily dosing)

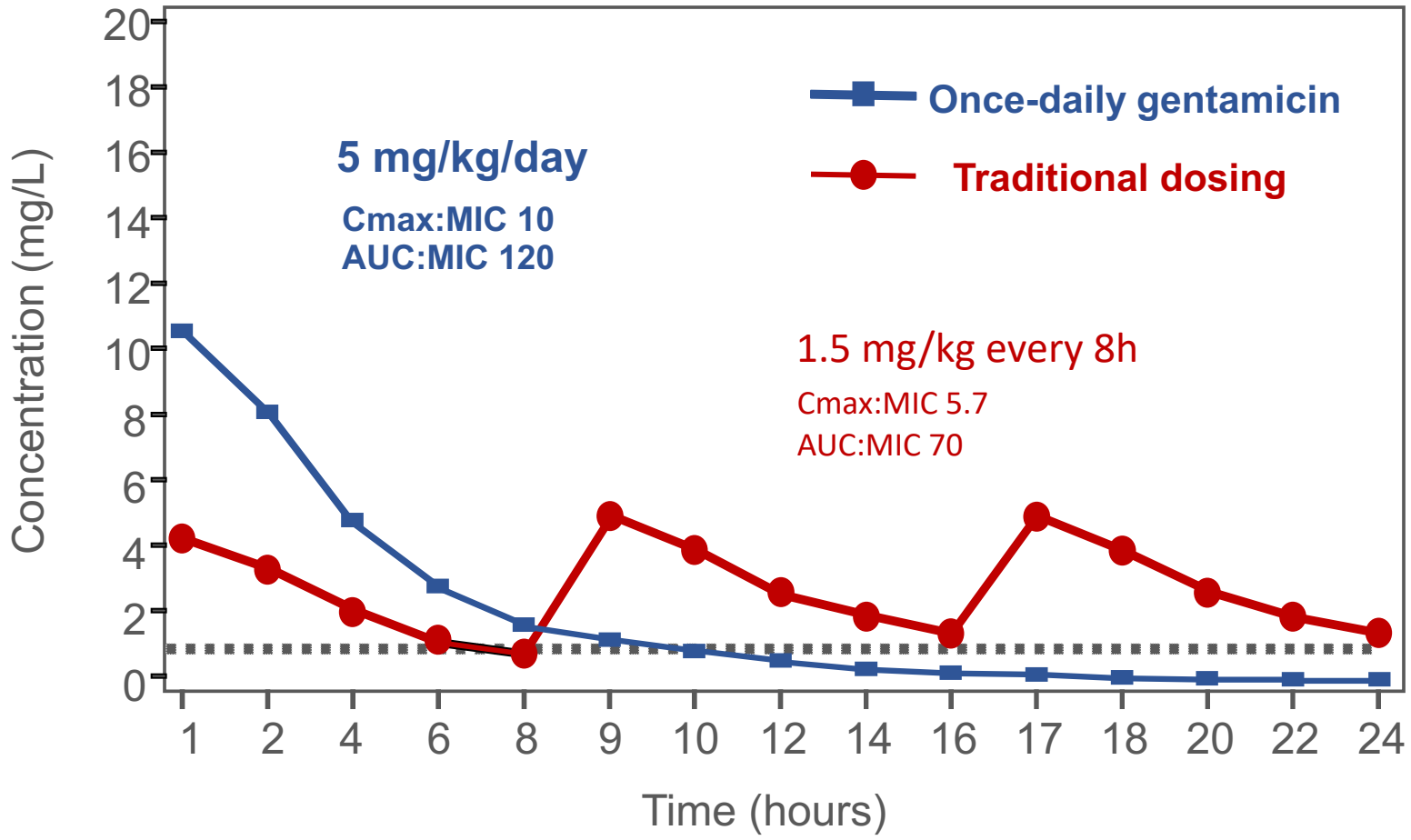


Drusano G et al. Clin Infect Dis 2007;45:753-760.; Kashuba et al. Antimicrob Agent Chemother 1999;43:623-9.

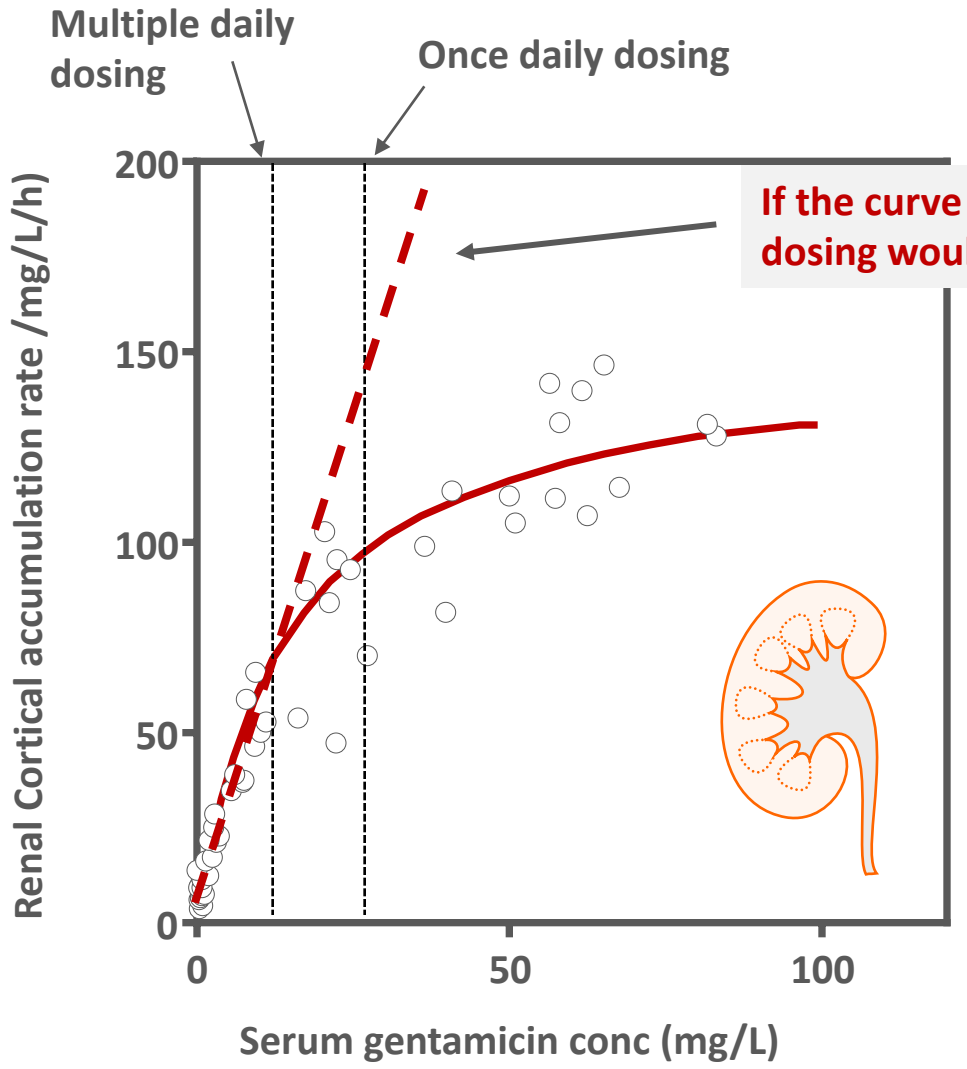
What can be done to improve gentamicin PK/PD?

- **Aminoglycosides have concentration-dependent PD characteristics**
  - Goal: Cmax:MIC > 10 or AUC/MIC > 150
- **Can we administer the same daily dose as a single daily dose to improve the Cmax:MIC ratio?**
- **Is there a concern for increased risk of nephrotoxicity or ototoxicity with a higher dose?**

Once-Daily gentamicin vs. traditional (q8h) Regimen



Renal cortex uptake of gentamacin is saturable

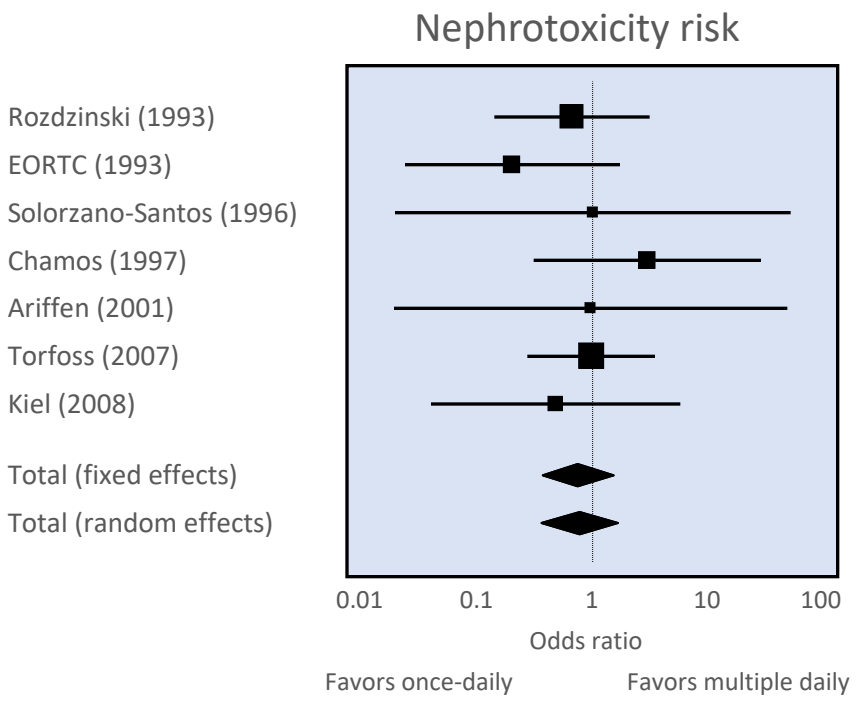


If the curve looked like this, once daily dosing would likely be more toxic

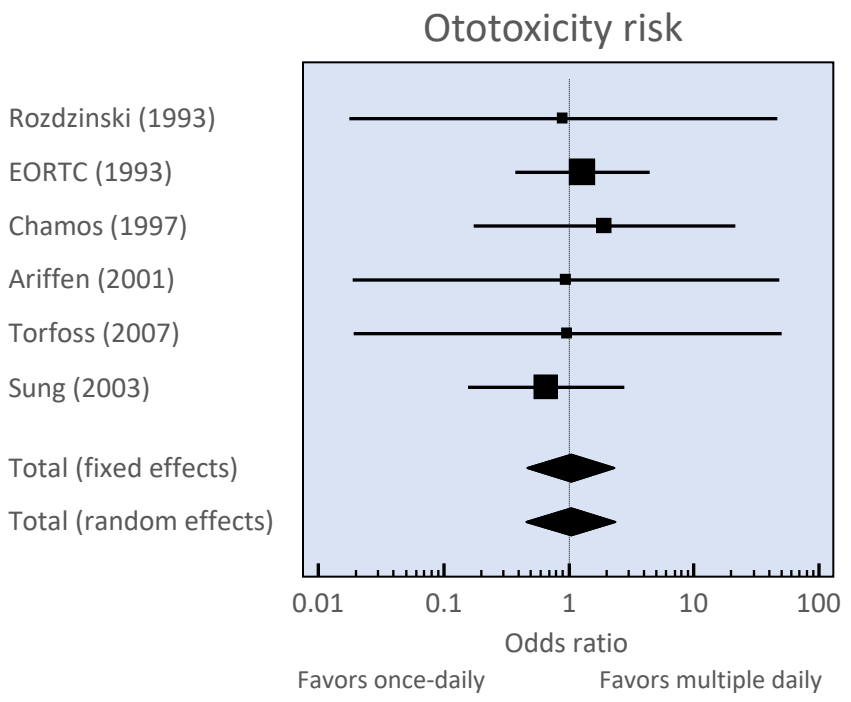
We would not predict markedly increased toxicity with single daily doses versus multiple daily doses

Giuliano et al. et al. J Pharm Exp Ther 1986;236:470-475.

Once versus multiple daily dosing of aminoglycosides for patients: a systematic review and meta-analysis



Trend of less nephrotoxicity



No difference

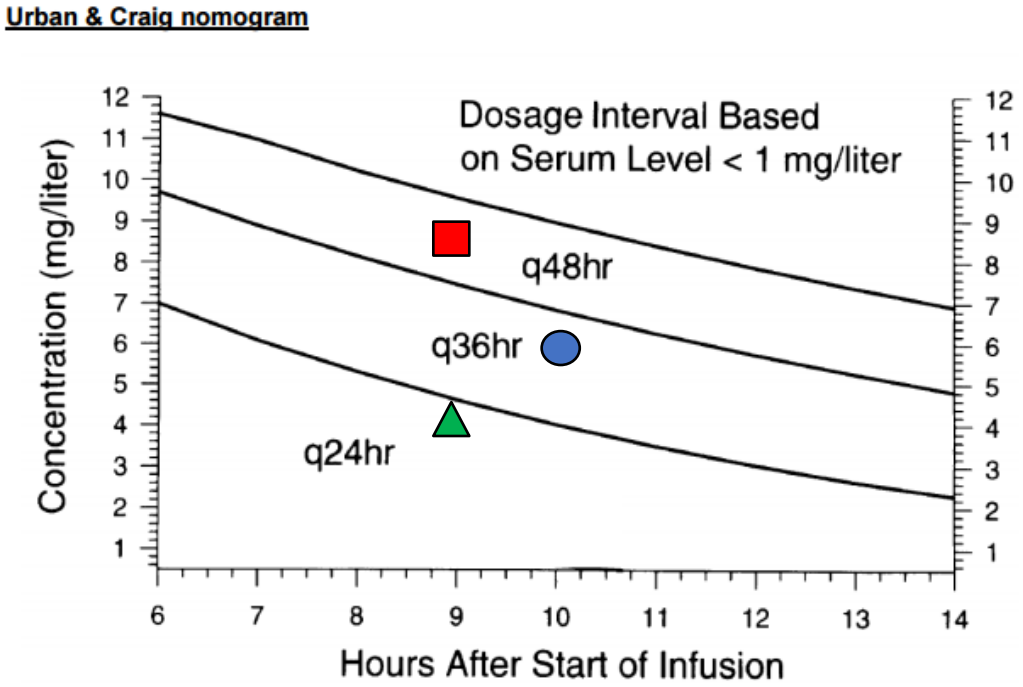
Mavros et al. J Antimicrb Chemother 2011;66:251-9.

Aminoglycosides

- Administration approximately the same daily dose of aminoglycosides once daily instead of multiple daily doses increases Cmax:MIC 5-fold, without increasing nephrotoxicity or ototoxicity

- Although superiority is not proven in all treatment populations, infrequent (once-daily) aminoglycoside dosing is considered as efficacious as traditional dosing with possibly less toxicity

Monitoring aminoglycoside regimens (duration of therapy > 3 days)



- Sample 1= 4 mcg/mL at 9 hours
- Sample 2= 6.8 mcg/mL at 10 hours
- Sample 3= 8.7 mcg/mL at 9 hours

Alternative dosing nomograms have been proposed using similar principles

Example Software for PK/PD Optimization of Antibiotic Dosing

for Gentamicin

Version: 0.95.5 beta / Built 20170531

Disclaimer:

TDMx has been created for personal use only. The use of any result
responsibility of the TDMx user. Therapeutic decision should not sole
does not replace clinical judgement. Although TDMx has been valida
the provided results.

When using TDMx, you automatically agree with this disclaimer and

Dr. Sebastian G. Wicha

c/o University of Hamburg, Germany

- Uses population PK models specific for drug/disease state
- Incorporates expected variability in pharmacokinetic estimates and allows dosing simulations for individual patient (monte-Carlo Simulation)
- Can adjust models based on results from TDM (Bayesian Dose Adaptation)
- Tells you not just what is possible PK/PD for your dosing, but what is probable based on your patient's characteristics
- Allows you to explore "what if" dosing scenarios using prior knowledge of pharmacokinetic studies

http://52.17.60.199/Gentamicin1/

Model recommended a 3 mg/kg dose when dosed at q8h interval (9 mg/kg over 24h), but there are problems….

PK/PD target(Cmax/MIC)

10

PK/Tox target(Cmin) [mg/L]

1

Date/time for next dose

26/02/2023/08:00

Infusion duration [h]

0.5

Minimum dose [mg/kg]

1.5

Feasible dosing intervals [h]

q8

Algorithm

Median (recommended)

Calculate

Format/Unit

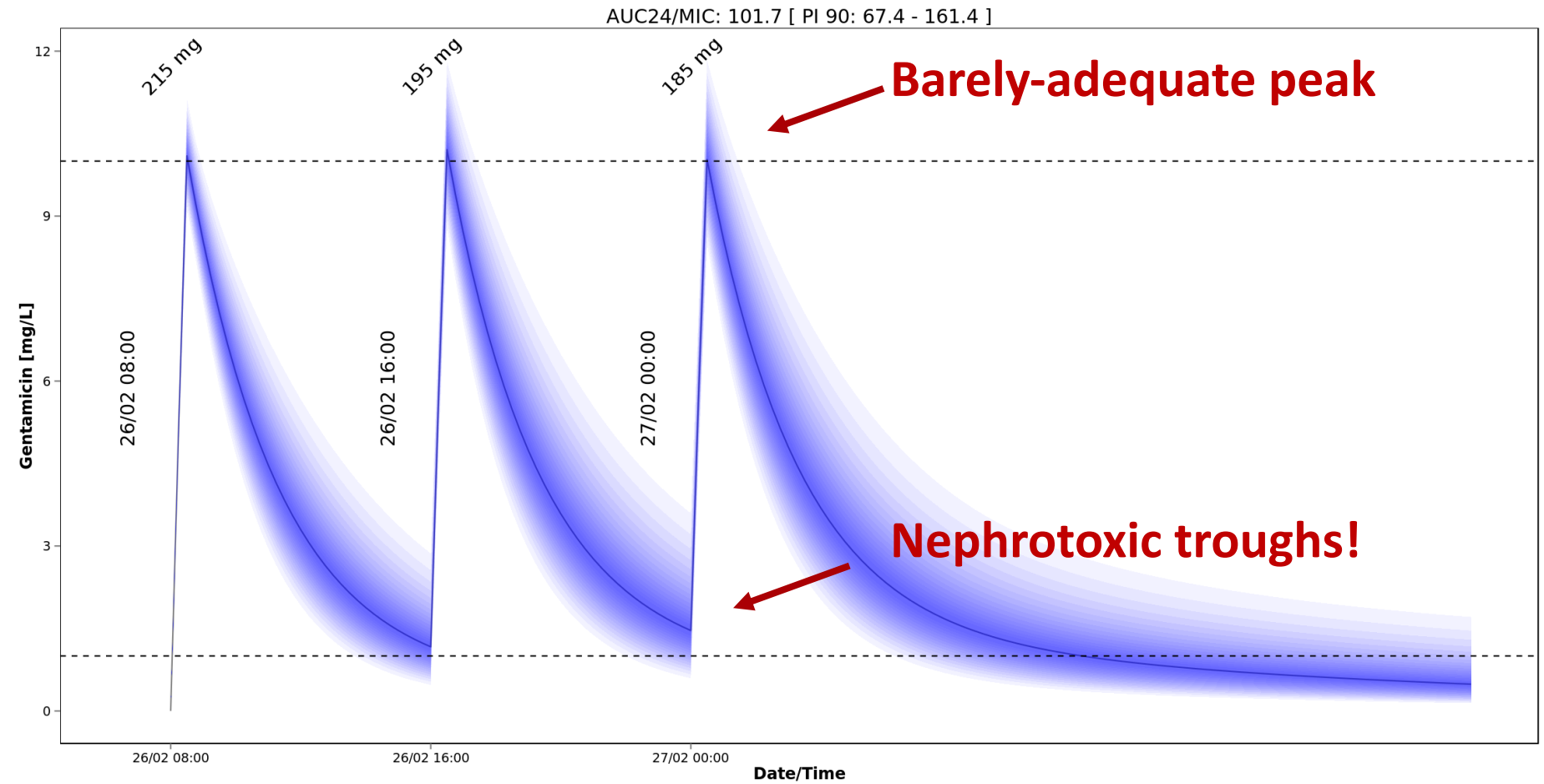
Time [dd/mm/yyyy/hh:mm]

Cmax/MIC [-]

Cmin [mg/L]

Infusion duration [h]

Probabilistic dosing scenarios (no drug measurements used/needed!)



No suitable doses found - consider modifying the target settings or provide more dosing intervals for evaluation!

PK/PD target(Cmax/MIC)

10

PK/Tox target(Cmin) [mg/L]

1

Date/time for next dose

26/02/2023/08:00

Infusion duration [h]

0.5

Minimum dose [mg/kg]

5

Feasible dosing intervals [h]

q24

Algorithm

Median (recommended)

Calculate

Format/Unit

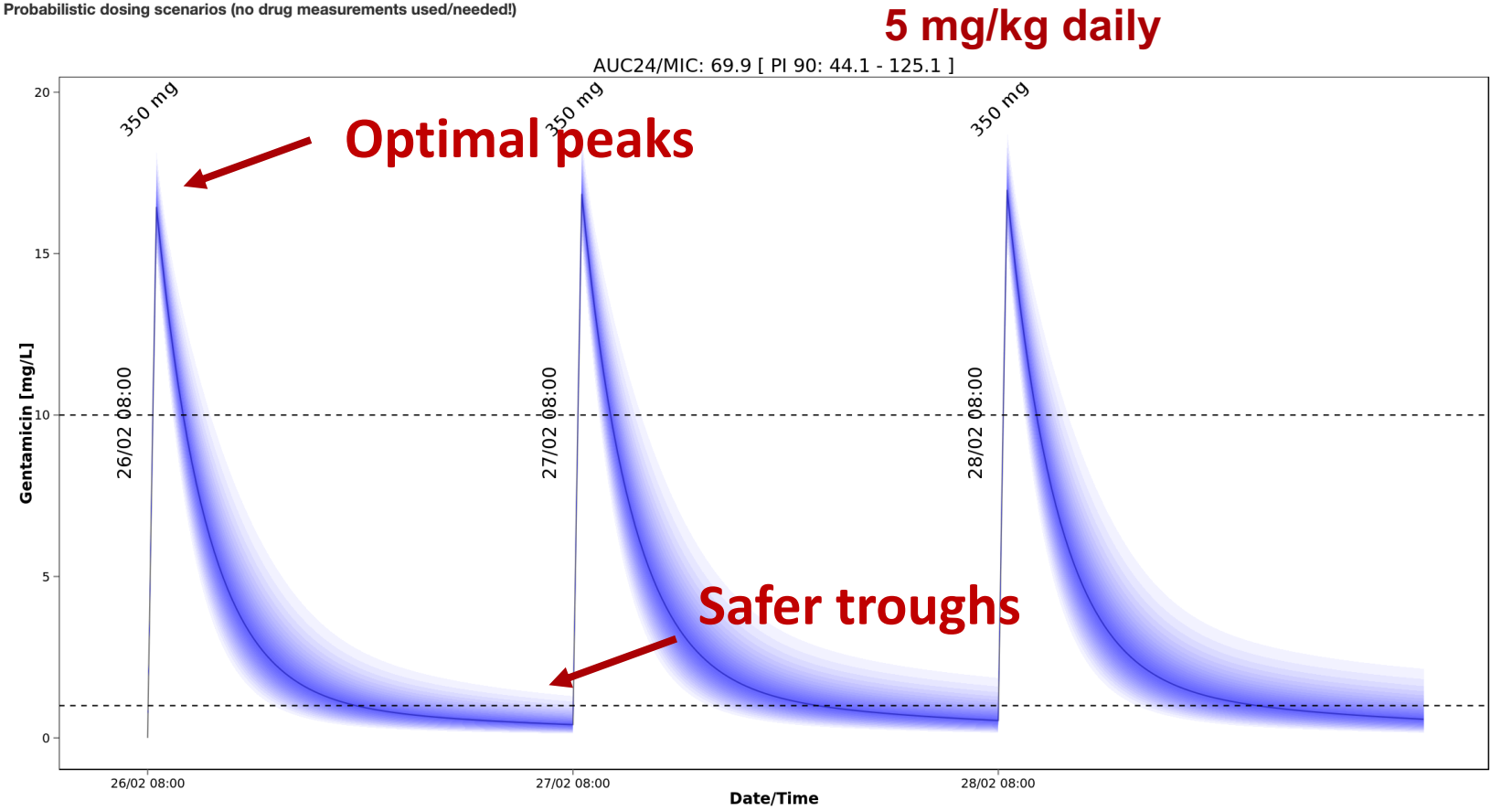
Time [dd/mm/yyyy/hh:mm]

Cmax/MIC [-]

Cmin [mg/L]

Infusion duration [h]

Probabilistic dosing scenarios (no drug measurements used/needed!)



Dosing interval: q 24 h / Target concentrations reached!

TDMx for Gentamicin | Disclaimer | 1. Patient | 2. Probabilistic Dosing | 3. Bayesian Dosing | 4. Optimise Sampling | Advanced Opt.

Demographics

Age [yrs.] 35 | Weight [kg] 70 | Height [cm] 170

Sex: male

Dose [mg] | Infusion dur. [h]

Time	Dose	Duration
25/02/2023/08:00	350	0.5
26/02/2023/08:00	350	0.5
27/02/2023/08:00	350	0.5

+ -

Dosing interval (for next dose) [h]: 24

Laboratory

Serum creatinine [mg/dL]

Time	cCreatinine
25/02/2023/13:00	0.9

+ -

MIC [mg/L]: 1

Measured gentamicin [mg/L]

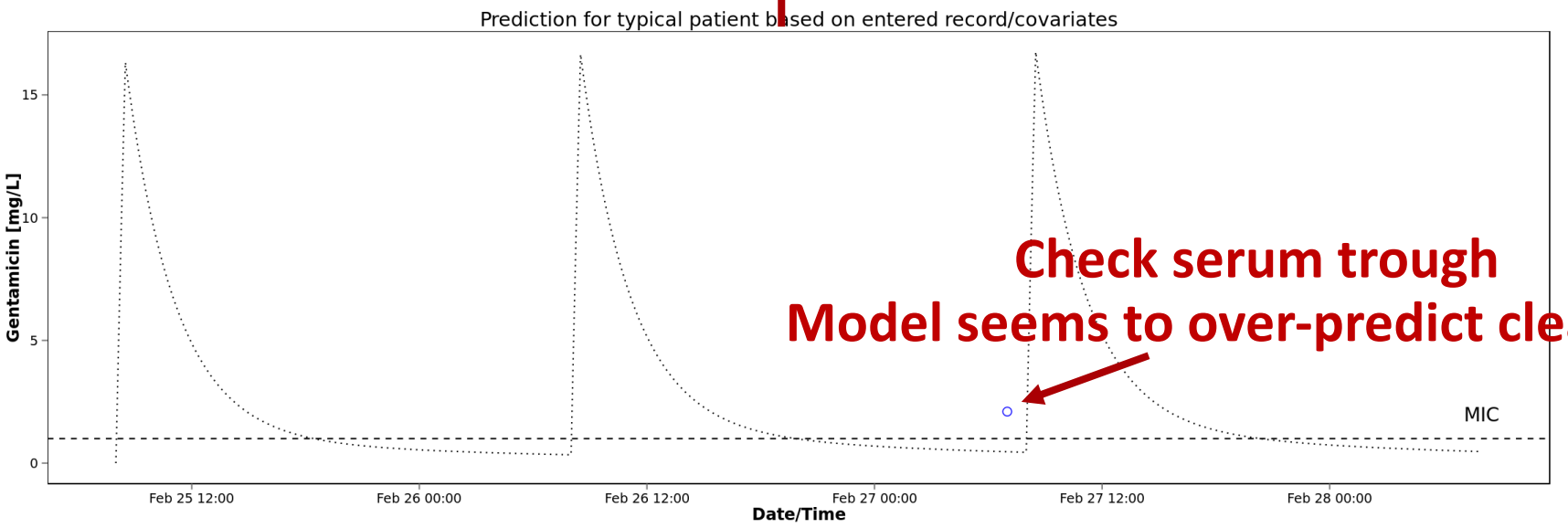
Time	cGentamicin
27/02/2023/07:00	2.1

+ -

Time [dd/mm/yyyy/hh:mm]

Dose [mg]

Infusion duration [h]



Check serum trough
Model seems to over-predict clearance

Bayesian dosing uses data from TDM to adjust model;
Providing more accurate individual predictions for the patient

PK/PD target(Cmax/MIC)

10

PK/Tox target(Cmin) [mg/L]

1

Date/time for next dose

26/02/2023/08:00

Infusion duration [h]

0.50

Minimum dose [mg/kg]

5

Feasible dosing intervals [h]

q24

Calculate

Format/Unit

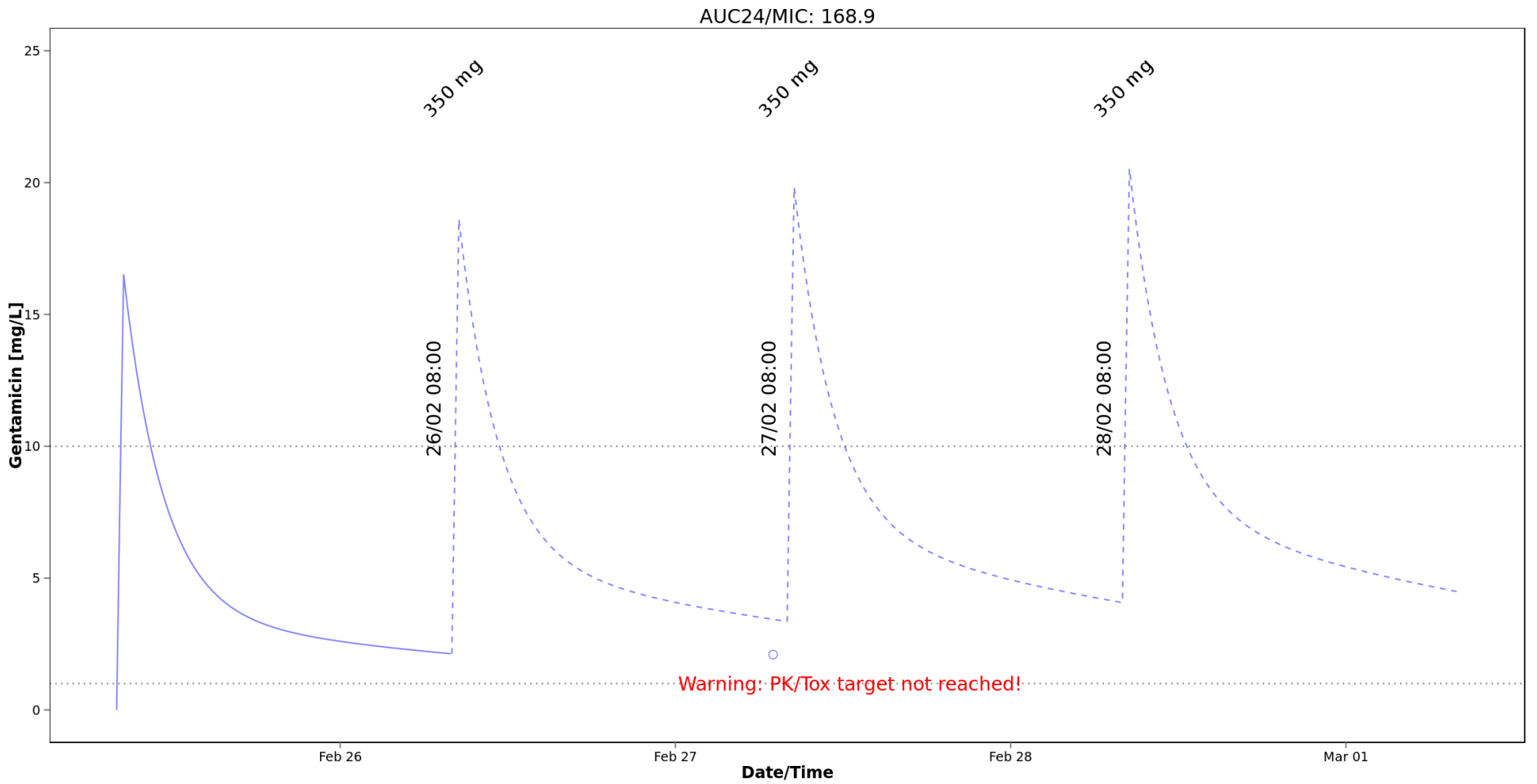
Time [dd/mm/yyyy/hh:mm]

Cmax/MIC [-]

Cmin [mg/L]

Infusion duration [h]

Prediction of next dose based on individual patient (using Bayesian estimates)



No suitable doses found - consider modifying the target settings or provide more dosing intervals for evaluation!

How is this patient different from the ”mean population” patient for gentamicin?

	Parameter	Unit	Description	Typical	Individual
1	CL	[L/h]	Drug Clearance	5.33	3.12
2	V1	[L]	Volume of Distribution	19.60	19.70
3	k12	[/h]	Transfer rate constant to peripheral compartment	0.09	0.16
4	k21	[/h]	Transfer rate constant to central compartment	0.07	0.09
5	AUC	[mg/L*h]	AUC (from first to last dose + dosing interval)		288.60
6	AUC 24h	[mg/L*h]	(average) AUC24h		96.20
7	PK/PD	[-]	(average) AUC24h / MIC		96.20

TDMx for Gentamicin | Disclaimer | 1. Patient | 2. Probabilistic Dosing | 3. Bayesian Dosing | 4. Optimise Sampling | Advanced Opt.

PK/PD target(Cmax/MIC)

10

PK/Tox target(Cmin) [mg/L]

1

Date/time for next dose

28/02/2023/08:00

Infusion duration [h]

0.50

Minimum dose [mg/kg]

5

Feasible dosing intervals [h]

q24 q36 q48

Calculate

Format/Unit

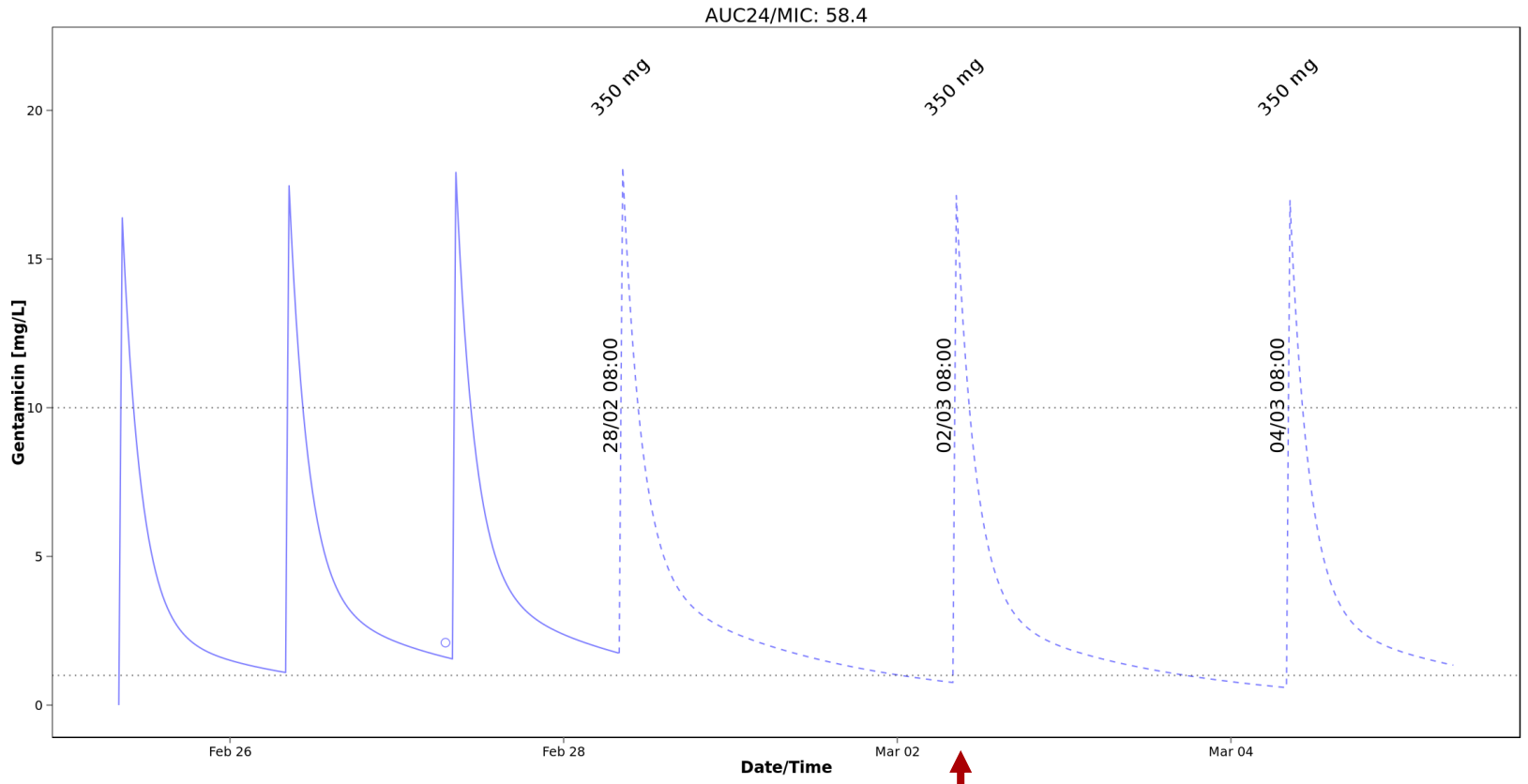
Time [dd/mm/yyyy/hh:mm]

Cmax/MIC [-]

Cmin [mg/L]

Infusion duration [h]

Prediction of next dose based on individual patient (using Bayesian estimates)



Dosing interval: q 48 h / Target concentrations reached!

Maintain daily dose, extend interval to 48h

Software-assisted dosing

- Available on computer desktop, some applications coming to smartphone platforms
- Based on population PK models for specific patient types
  - *Pay attention to the patient population used to develop the model!*
- Best models can adjust PK estimates and dosing recommendations based on therapeutic drug monitoring results (Bayesian estimation)
- Models are only a general guide-recommendation must not be followed blindly!
- Dosing models may not be available for your specific patient situation
- Link to dosing models at www.padovaid.com

Case Cont.

- You change the patient's gentamicin dose to 350 mg every 24 hours and will monitor using the nomogram on the previous slide

- Unfortunately, the patient's fever persistens, and your unit chief wants to add vancomycin to cover *S. aureus*

- You are told to use a dose that will immediately achieve and maintain a trough serum concentration of 20 to 30 mg/L.

Pharmacodynamic parameters predictive of outcomes in animals and humans

	C_{max}/MIC	AUC/MIC	T>MIC
Examples	Aminoglycosides Fluoroquinolones Polymyxins **Also predicted by AUC:MIC**	Azithromycin Fluoroquinolones Ketolides Linezolid Daptomycin Vancomycin Tigecycline	Penicillins Cephalosporins Carbapenems Monobactams Macrolides
Organism kill	Concentration-dependent	Concentration and time dependent	Time-dependent
Dosing goal	Maximize exposure	Maximize exposure	Optimize duration of exposure

Drusano & Craig. *J Chemother* 1997;9:38–44 ; Drusano et al. *Clin Microbiol Infect* 1998;4 (Suppl. 2):S27–S41,

Vancomycin pharmacodynamics

- **PK:PD Index associated with efficacy**
  - (Total drug) AUC/MIC > 400
- **Serum trough concentrations correlate with AUC**
  - In the past, monitoring of trough serum concentrations was recommended to ensure adequate dosing, reduce toxicity in critically-ill patients
    - Trough concentrations of 15-20 mg/L (roughly equivalent to AUC > 400) were recommended during the treatment of infectious caused by methicillin-resistant *Staphylococcus* aureus with MIC up to 1 mg/L
    - However, nephrotoxicity risk increases when troughs > 30 mg/L
  - **How can you dose to a trough of 15-20 but reduce the risk of nephrotoxicity?**

Rybak et al. Am J Health-System Pharm 2009;66:82-98. Rybak MJ, et al. Pharmacotherapy **2020**; 40:363–367.

How to calculate a vancomycin dose (manually)

- Target concentration (CP)= 20 mg/L
- Age: 45 years, CrCL=103 mL/min, 70 kg
- Vd: 0.75 L/kg (from med. literature)
- $CL_{vancomycin}$: 0.65 x$CrCL_{est}$ (Cockroft Gault)

$$CP\,(mg/L) = \frac{Loading\ dose\,(mg/kg)}{Vd\,(L/kg)}$$

$$Loading\ dose\ (mg/kg) = 20\,mg/L\,x\,0.75\,L/kg$$

$$Loading\ dose\ (mg/kg) = 15\,mg/kg$$

$$Loading\ dose = 1050\,mg\ or\ 1000\,mg$$

$$Infusion\ rate\,(mg/\min) = CP_{target}\,(mg/L)\,x\,[CL_{vancomycin}\,(mL/\min)]$$

$$Infusion\ rate\,(mg/\min) = 20\,mg/L\,x\,[0.65\,x\,CrCl\,(mL/\min)]$$

$$Infusion\ rate\,(mg/\min) = 20\,mg/L\,x\,[0.65\,x\,103\,(ml/\min)]$$

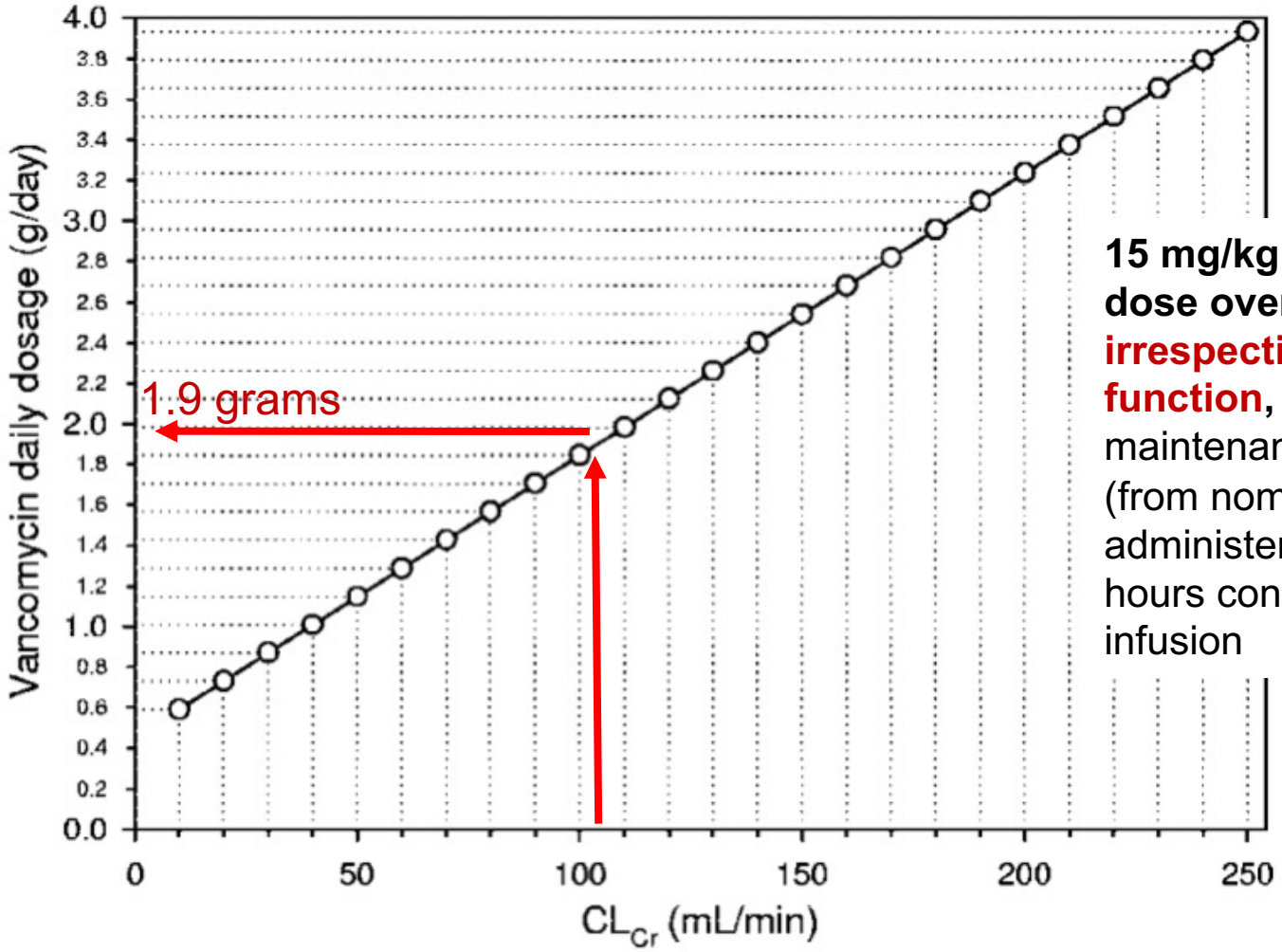
$$Infusion\ rate\,(mg/\min) = 1.34\,mg/\min = 80.3\,mg/hr = 1928\,mg/day$$

Nomogram for continuous infusion dosing of vancomycin to rapidly achieve and maintain a trough of 20 mg/L in critically-ill patients

Therapeutic
drug monitoring to
confirm near 20 mg/L

To estimate AUC:

20 mg/L x 24h= 480 mg/L·h



15 mg/kg loading dose over 2 hours irrespective of renal function, then maintenance dose (from nomogram) is administered over 24 hours continuous infusion

Pea et al. Antimicrob Agent Chemother 2009;53:1863-7.

Method	Pro	Con	Comments
Trapezoidal equations (see vancomycin AUC dosing calculator)	Log-linear equations used to calculate true peak and trough based on measured peak and trough levels	Steady state must be achieved; 2 measurements required: peak and trough	Once AUC_{24} for particular dose and interval is determined, adjustment of dose and interval for subsequent doses is proportional ratio. See AUC Dosing Fundamentals and Calculations
Trough level	No calculation required	Poor proxy for AUC_{24}; target may be achieved with tough < 15	Preferred for meningitis, CNS infections; unstable renal function; diseases with target trough 10-15
Bayesian	Calculation may be based on single level, including pre-steady state. Adaptive to physiologic changes	Software tends to be expensive	Can work with single level, but better results with peak and trough measurements
Continuous infusion	Simple calculation based on 1-2 random levels	Requires full-time use of dedicated IV line	AUC_{24} = steady state level x 24

- **Treatment failure.**
  - Regardless of MIC vs MRSA, if blood cultures remain positive for 2-3 days with clinical evidence of ongoing "sepsis", and no undrained abscesses, consider patient a Vancomycin treatment failure. In retrospective study of patients with MRSA bacteremia, correlation of Vancomycin treatment failure with Vancomycin trough levels < 15 µg/mL and MIC > 1 µg/mL (Clin Infect Dis 52:975, 2011).

Adult Dose

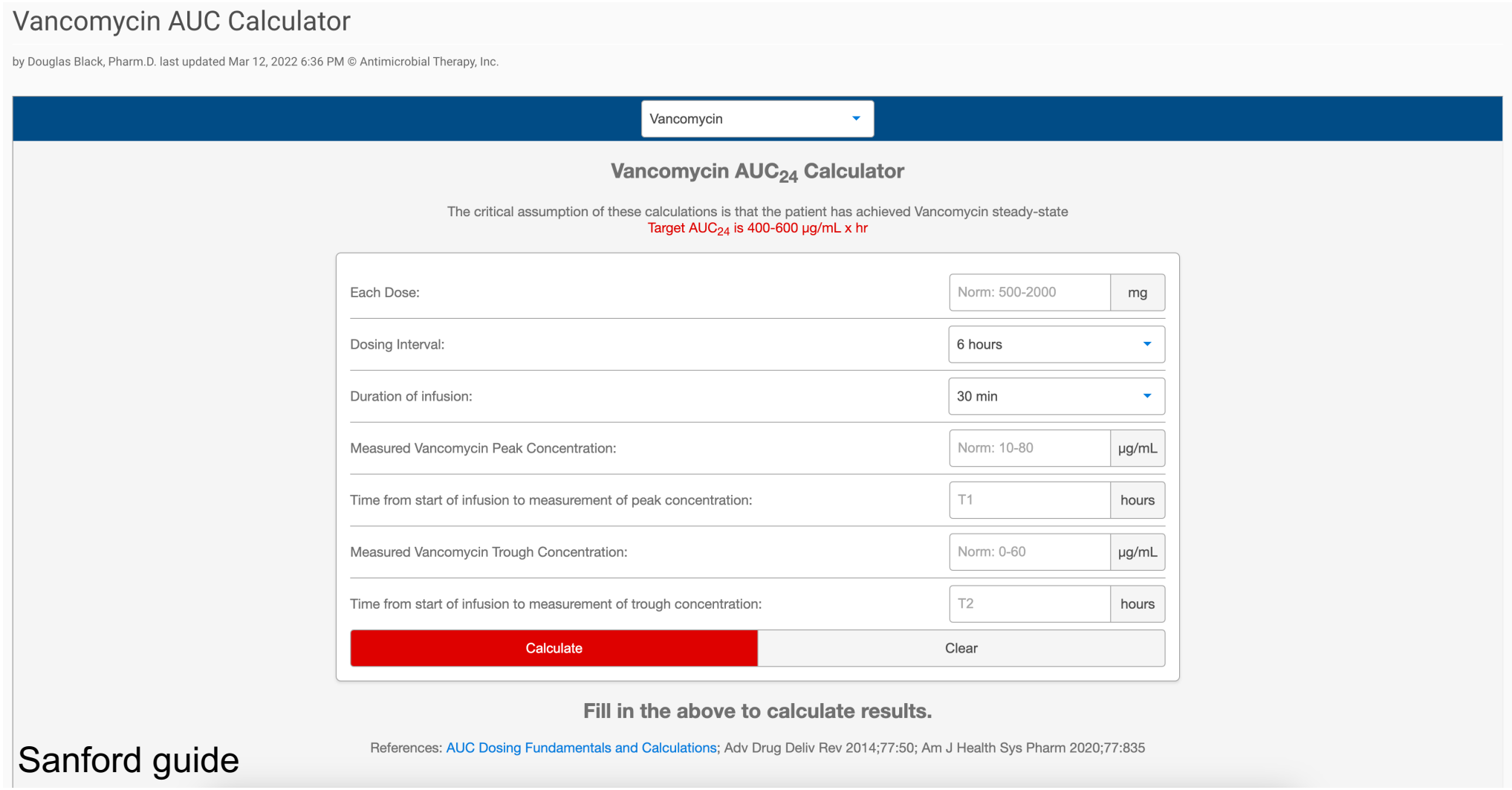
- **IV formulation - Intermittent dosing**
  - **Target AUC_{24} serum levels of 400-600 µg/mL x hr**
    - **Allow 24-48 hours to achieve steady state, then measure peak and trough serum levels**
    - **Use vancomycin AUC dosing calculator** (for explanatory notes and formulas, see AUC Dosing Fundamentals and Calculations) **to:**
      - **Calculate initial AUC_{24} based on measured peak and trough levels**
      - **Adjust dose or interval for subsequent doses**
  - Loading dose:
    - For serious infection, critical illness whether intermittent or continuous infusion
    - Shortens time to achieve steady state serum level
    - **20-30 mg/kg IV (based on actual body weight) infused at rate of 10-15 mg/min (maximum 3 gm)**
  - Maintenance dose
    - **15-20 mg/kg IV over 60 min q8-12h adjusted to achieve target AUC_{24} of 400-600 µg/mL x hr**
    - Intermittent dosing: Start first maintenance dose at the end of the first dosing interval
    - Continuous infusion: Start maintenance dosing immediately after completion of infusion of the loading dose
  - Morbid obesity
    - See "Other Adjustment" below
- **IV Formulation - Continuous infusion**
  - Loading dose: 15-20 mg/kg (infusion rate 10-15 mg/min)
  - Continuous infusion dose: 30-40 mg/kg (up to 60 mg/kg) over 24 hours daily
  - Start continuous infusion immediately after completion of infusion of the loading dose
  - Morbid obesity: inadequate data on continuous infusion in this population
- **IV Formulation - Intrathecal dosing**
  - Adult: 10-20 mg/day
  - Target CSF concentration is 10-20 µg/mL
- **Oral Formulation (po) dosing:**

“2100 mg (30 mg/kg) loading dose over 140 min; then 1050 mg (15 mg/kg) every 8 hours over 60 min. Check vancomycin peak and trough after 3rd dose. “

Sanford Guide

Vancomycin AUC monitoring

Monitoring only based on troughs may results in overdosing for a proportion of patients



Sanford guide

Software recommended dosing

Patient ID

Patient | Laboratory | Dosing

Dose [mg] | Infusion dur. [h]

Date/Time	Dose	Dur.	Nr.	Int.
26/02/2023/06:00	2100.00	2.50	1.00	8.00
26/02/2023/17:00	1050.00	1.00	1.00	8.00
27/02/2023/01:00	1050.00	1.00	1.00	8.00
27/02/2023/09:00	1050.00	1.00	1.00	8.00

+ -

Dose optimization

Target

(•) AUC24h/MIC ( ) Trough

Target value

500

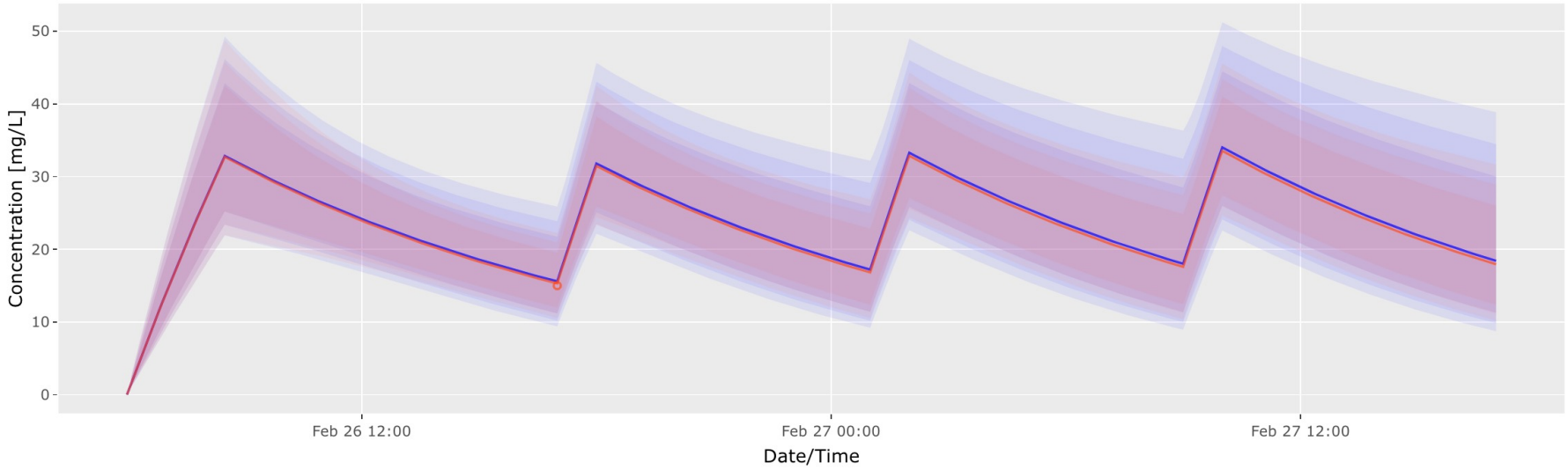
Optimization type

( ) First dose (•) Add dose

CALCULATE

SAVE INPUT DATA

Single model | Model averaging



Plot: (•) Concentration-Time ( ) AUC

Options: [x] Population [x] Individual [x] Variability

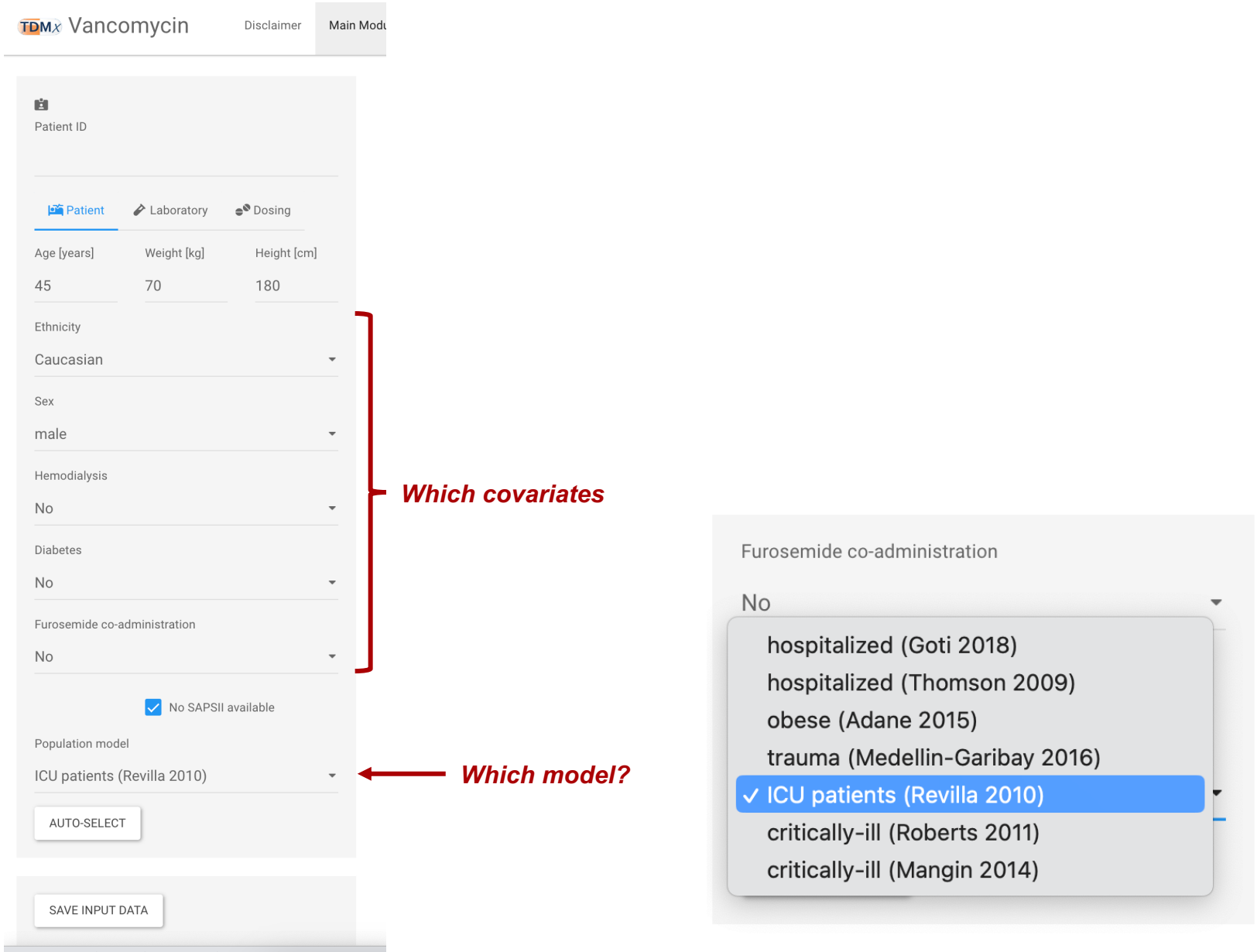
Resolution: (•) HD ( ) SD

Show 10 entries

	Date/Time [d/m/y/h:m]	Rel. Time [h]	Dose [mg]	Obs. [mg/L]	Pop. Pred. [mg/L]	Ind. Pred. [mg/L]	Creat. CL [mL/min]	Ind. CL [L/h]	Ind. V1 [L]	Ind. V2 [L]	Ind. AUC [mg/L*h]	Ind. AUC24h/MIC [-]
1	26/02/2023/06:00	0	2100		0	0	83.28	5.139	57.52	0	0	
2	26/02/2023/17:00	11	0	15	15.59	15.31	83.28	5.139	57.52	0		
3	26/02/2023/17:00	11	1050		15.59	15.31	83.28	5.139	57.52	0	237.3	517.7
4	27/02/2023/01:00	19	1050		17.21	16.84	83.28	5.139	57.52	0	187.3	561.9
5	27/02/2023/09:00	27	1050		18.02	17.58	83.28	5.139	57.52	0	196	588
6	27/02/2023/17:00	35	0		18.42	17.95	83.28	5.139	57.52	0	200.2	600.6

Showing 1 to 6 of 6 entries

Previous 1 Next


TDMx Vancomycin
Disclaimer
Main Modu
Patient ID
Patient
Laboratory
Dosing
Age [years]
45
Weight [kg]
70
Height [cm]
180
Ethnicity
Caucasian
Sex
male
Hemodialysis
No
Diabetes
No
Furosemide co-administration
No
No SAPSII available
Population model
ICU patients (Revilla 2010)
AUTO-SELECT
SAVE INPUT DATA
Which covariates
Which model?
Furosemide co-administration
No
hospitalized (Goti 2018)
hospitalized (Thomson 2009)
obese (Adane 2015)
trauma (Medellin-Garibay 2016)
ICU patients (Revilla 2010)
critically-ill (Roberts 2011)
critically-ill (Mangin 2014)

Adding TDM results, we see we are overdosing patient…

TDMx Vancomycin | Disclaimer | Main Module | Settings

Patient ID

Patient | Laboratory | Dosing

Serum creatinine

Unit Creatinine

(•) mg/dL ( ) umol/L

Date/Time	Creatinine
25/02/2023/08:00	0.90

\+ -

Albumin [g/dL]

[x] Not available

Serum urea nitrogen [mg/dL]

[x] Not available

MIC [mg/L]

1

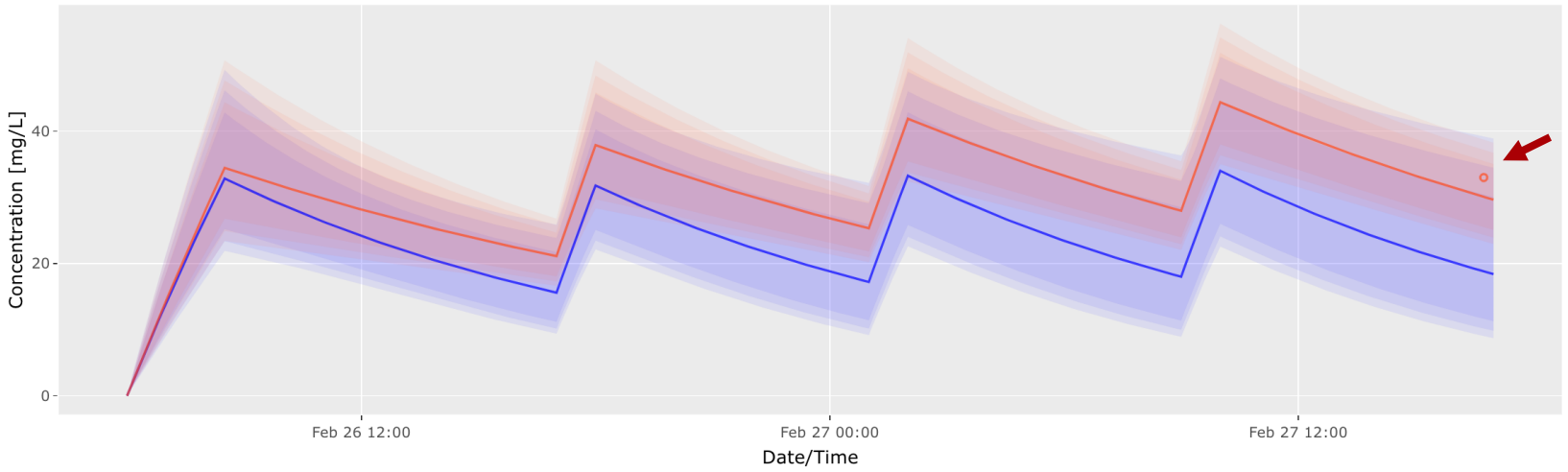
TDM measurements [mg/L]

Date/Time	Vancomycin
27/02/2023/16:45	33.00

\+ -

SAVE INPUT DATA

Single model | Model averaging



Plot: (•) Concentration-Time ( ) AUC

Options: [x] Population [x] Individual [x] Variability

Resolution: (•) HD ( ) SD

Show 10 entries

	Date/Time [d/m/y/h:m]	Rel. Time [h]	Dose [mg]	Obs. [mg/L]	Pop. Pred. [mg/L]	Ind. Pred. [mg/L]	Creat. CL [mL/min]	Ind. CL [L/h]	Ind. V1 [L]	Ind. V2 [L]	Ind. AUC [mg/L*h]	Ind. AUC24h/MIC [-]
1	26/02/2023/06:00	0	2100		0	0	83.28	3.271	56.74	0	0	
2	26/02/2023/17:00	11	1050		15.59	21.11	83.28	3.271	56.74	0	275.7	601.5
3	27/02/2023/01:00	19	1050		17.21	25.32	83.28	3.271	56.74	0	248	744
4	27/02/2023/09:00	27	1050		18.02	27.98	83.28	3.271	56.74	0	274.9	824.7
5	27/02/2023/16:45	34.75	0	33	18.82	30.08	83.28	3.271	56.74	0		
6	27/02/2023/17:00	35	0		18.42	29.65	83.28	3.271	56.74	0	292	876

Showing 1 to 6 of 6 entries

Previous 1 Next

Individualized dosing adjustment recommendations then recheck TDM

TDMx Vancomycin Disclaimer Manual Settings

Patient ID

Patient | Laboratory | Dosing

Serum creatinine

Unit Creatinine

mg/dL | umol/L

Date/Time	Creatinine
25/02/2023/08:00	0.90

+ -

Albumin [g/dL]

Not available

Serum urea nitrogen [mg/dL]

Not available

MIC [mg/L]

1

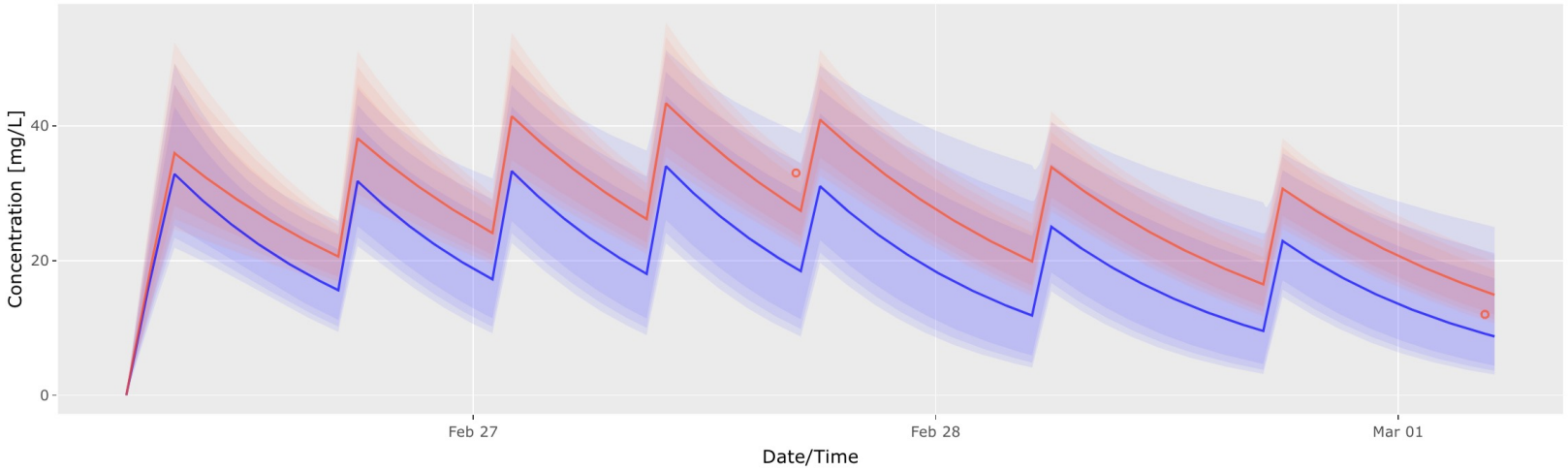
TDM measurements [mg/L]

Date/Time	Vancomycin
27/02/2023/16:45	33.00
1/03/2023/04:30	12.00

+ -

SAVE INPUT DATA

Single model | Model averaging



Plot: Concentration-Time | AUC

Options: Population | Individual | Variability

Resolution: HD | SD

Show 10 entries

	Date/Time [d/m/y/h:m]	Rel. Time [h]	Dose [mg]	Obs. [mg/L]	Pop. Pred. [mg/L]	Ind. Pred. [mg/L]	Creat. CL [mL/min]	Ind. CL [L/h]	Ind. V1 [L]	Ind. V2 [L]	Ind. AUC [mg/L*h]	Ind. AUC24h/MIC [-]
1	26/02/2023/06:00	0	2100		0	0	83.28	3.537	53.86	0	0	
2	26/02/2023/17:00	11	1050		15.59	20.58	83.28	3.537	53.86	0	280.4	611.8
3	27/02/2023/01:00	19	1050		17.21	24.08	83.28	3.537	53.86	0	243.5	730.5
4	27/02/2023/09:00	27	1050		18.02	26.16	83.28	3.537	53.86	0	265.3	795.9
5	27/02/2023/16:45	34.75	0	33	18.82	27.84	83.28	3.537	53.86	0		
6	27/02/2023/17:00	35	850		18.42	27.38	83.28	3.537	53.86	0	278.2	834.6
7	28/02/2023/05:00	47	850		11.84	19.87	83.28	3.537	53.86	0	354.8	709.6
8	28/02/2023/17:00	59	850		9.538	16.45	83.28	3.537	53.86	0	292.4	584.8
9	01/03/2023/04:30	70.5	0	12	9.127	15.4	83.28	3.537	53.86	0		

Case Cont.

- The next day, the patient had one episode of fever despite the addition of the vancomycin
- The patient's pneumonia is stable
- However, tracheal aspirate cultures from 2 days ago:
  - *P. aeruginosa*, meropenem MIC 4 mg/L (R)
  - Sensitive only to gentamicin, amikacin, ceftolozane/tazobactam and colistin
- The patient's renal function is also worsening
  - Serum creatinine 1.4 mg/dL (estimated CrCl 66 mL/min)
- Your chief does not want to start colistin, and the pharmacy says ceftolozane/tazobactam will not be available until next week
- The chief tells you to give "high-dose" PK/PD optimized meropenem

Pharmacodynamic parameters predictive of outcomes in animals and humans

	C_{max}/MIC	AUC/MIC	T>MIC
Examples	Aminoglycosides Fluoroquinolones Polymyxins **Also predicted by AUC:MIC**	Azithromycin Fluoroquinolones Ketolides Linezolid Daptomycin Vancomycin Tigecycline	Penicillins Cephalosporins Carbapenems Monobactams Macrolides
Organism kill	Concentration-dependent	Concentration and time dependent	Time-dependent
Dosing goal	Maximize exposure	Maximize exposure	Optimize duration of exposure

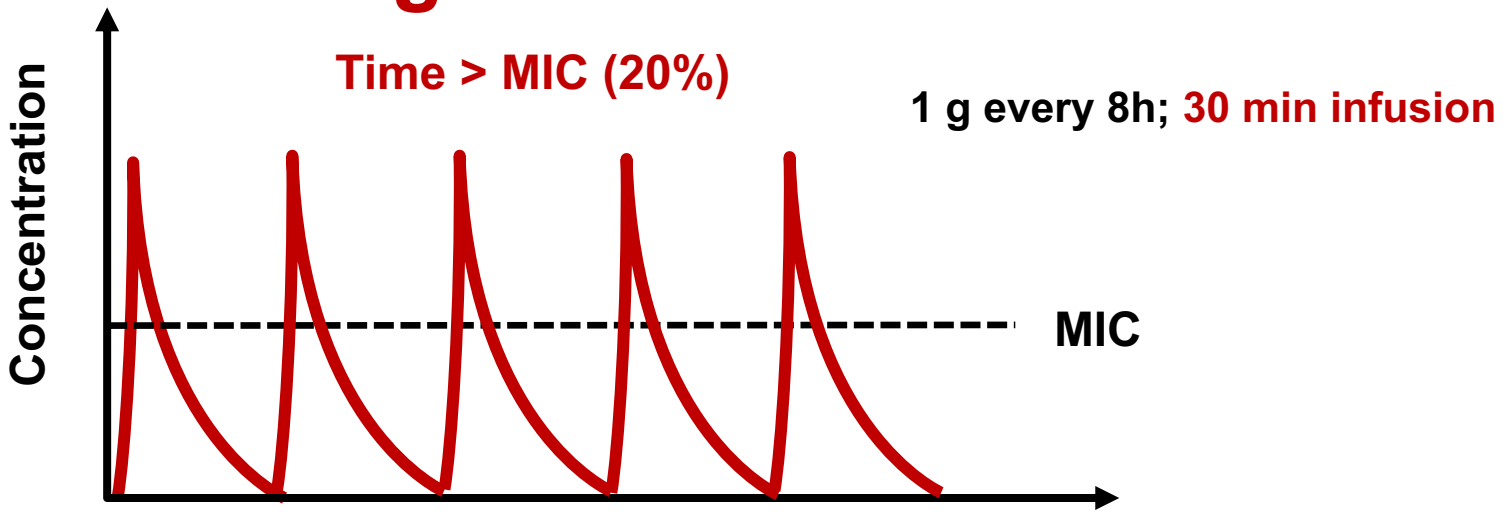
Drusano & Craig. *J Chemother* 1997;9:38–44 ; Drusano et al. *Clin Microbiol Infect* 1998;4 (Suppl. 2):S27–S41,

Beta-Lactams: Targeted PD Exposure

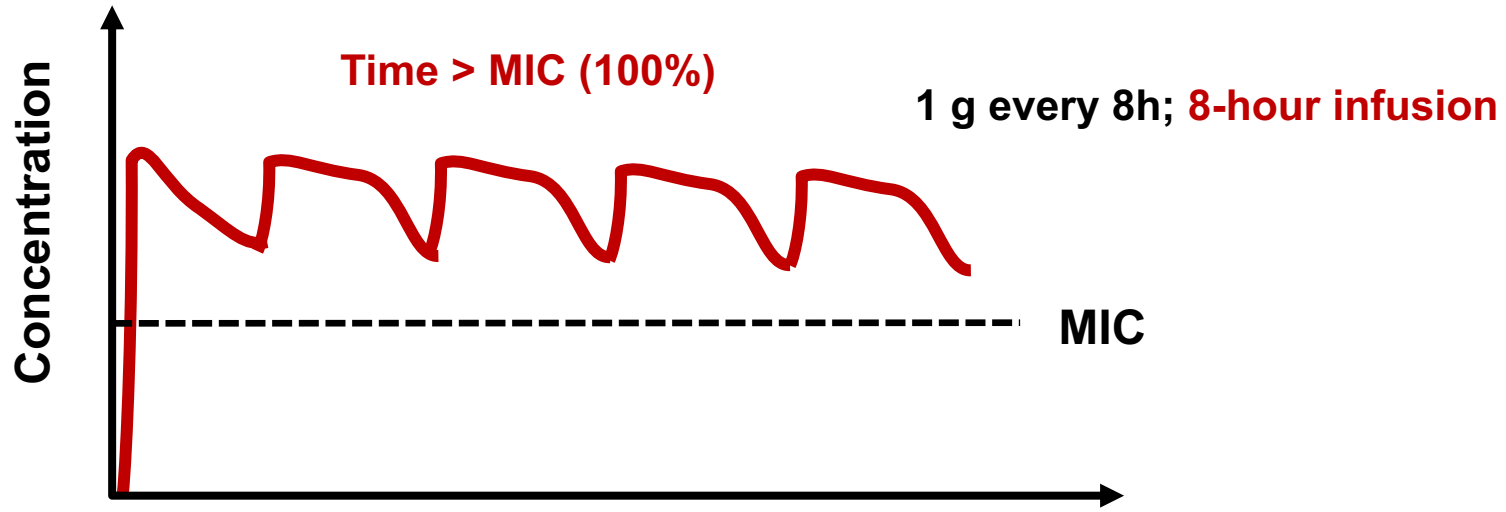
- The optimum level of exposure varies for different agents within the beta-lactam class
- Required %T>MIC for efficacy:
  - ~ 50%–70% for cephalosporins
  - ~ 50% for penicillins
  - ~ 40% for carbapenems
- Reason: Acetylation of target β-lactam binding proteins occurs at low multiples of MIC, and inhibition (and reversal) takes time
  - This time is shorter than the dosing interval but varies among different β-lactams
- In critically-ill patients, many advocate ~ 100% T> MIC or even 4xMIC

Drusano GL. *Clin Infect Dis.* 2003;36(suppl 1):S42-S50.

This is what is occurring…



We want this…



Example: Meropenem dosing for *P. aeruginosa* (MIC 4 mg/L)

- Patient already receiving meropenem 1 gram every 8h in 30 min infusions
- Target initial concentration (CP)= 16 mg/L (4xMIC)
- Age: 45 years, CrCL=66 mL/min, 70 kg
- Vd: 0.38 L/kg (from med. literature)
- $CL_{meropenem}$: [0.078x59]+2.85 mL/hr

Loading dose not needed in this case-already on meropenem!

$$CP(mg/L) = \frac{Loading\ dose(mg/kg)}{Vd(L/kg)}$$

$$Loading\ dose\ (mg/kg) = 16mg/L\ x\ 0.38\ L/kg$$

$$Loading\ dose\ (mg/kg) = 6.08\,mg/kg \approx 6mg/kg$$

$$Loading\ dose = 420\,mg \sim 500mg$$

Example: Meropenem dosing for *P. aeruginosa* (MIC 4 mg/L)

- Target concentration (CP)= 16 mcg/mL
- Age: 45 years, CrCL=66 mL/min
- Vd: 0.38 L/kg (from med. literature)
- $CL_{meropenem}$: [0.078xCrCL]+2.85 mL/hr

Maintenance dose:

$$Infusion\,rate\,(mg/hr) = CP_{target}\,(mg/L)\,x\,[CL_{meropenem}\,(mL/hour)]$$

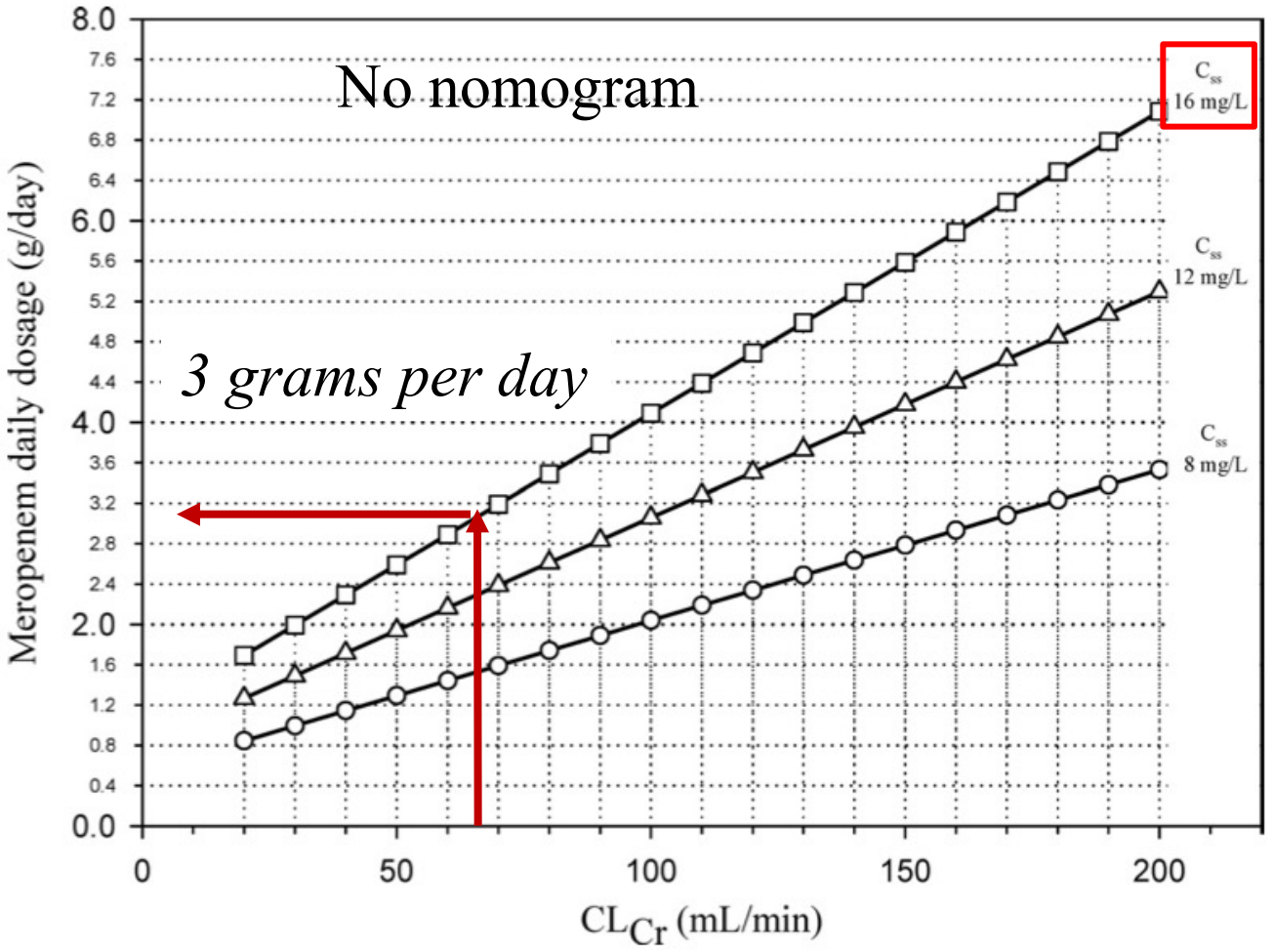
$$Infusion\,rate\,(mg/hr) = 16\,mg/L\,x\,([0.078\,xCrCl\,(ml/\min)] + 2.85)$$

$$Infusion\,rate\,(mg/hr) = 16\,mg/L\,x\,([0.078\,x\,66] + 2.85]$$

$$Infusion\,rate\,(mg/hr) = 127\,mg/hr = 3071\,mg/day \approx 3\,grams/day$$

1 gram could be infused over 8 hours 3x daily
(meropenem cannot be given over 24 hours infusion because of instability in IV bag)

Dosing Nomogram for Obtaining Optimal Meropenem Concentrations



1-2 gram loading dose over 30 min.

Continuous infusion started immediately thereafter

Bags must be changed every 8 hours

Pea et al. Antimicrob Agent Chemother 2012;56:6343.48.

Patient ID

Patient | Laboratory | Dosing

Serum creatinine

Unit Creatinine

mg/dL umol/L

Date/Time	Creatinine
25/02/2023/08:00	1.40

+ -

Albumin [g/dL]

Not available

MIC [mg/L]

4

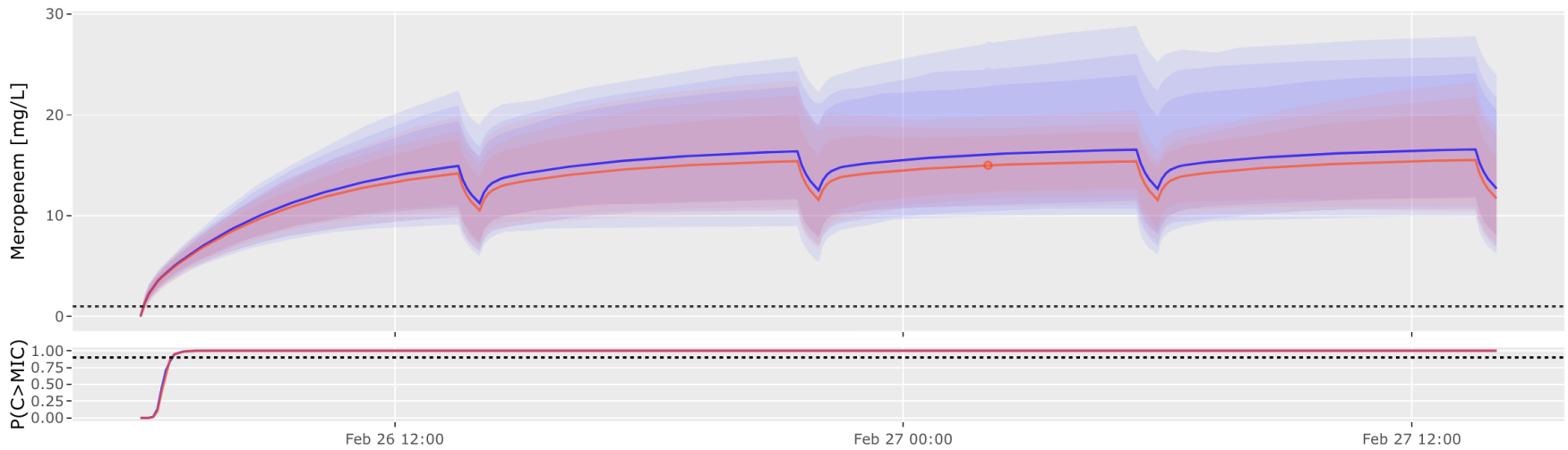
TDM measurements [mg/L]

Date/Time	Meropenem
27/02/2023/02:00	15.00

+ -

SAVE INPUT DATA

Single model



Plot

Concentration-Time

Display Options

Population Individual Variability

Resolution

HD SD

Show 10 entries

	Date/Time [d/m/y/h:m]	Rel. Time [h]	Dose [mg]	Rate [mg/h]	Obs. [mg/L]	Pop. Pred. [mg/L]	Ind. Pred. [mg/L]	eGFR [mL/min]	Ind. CL [L/h]	Ind. V1 [L]	Ind. V2 [L]	Ind. T>MIC [%]
1	26/02/2023/06:00	0	1000	133.333333333333		0	0	65.99	8.447	7.899	17.71	
2	26/02/2023/14:00	8	1000	133.333333333333		11.25	10.53	65.99	8.447	7.899	17.71	93.4
3	26/02/2023/22:00	16	1000	133.333333333333		12.52	11.58	65.99	8.447	7.899	17.71	100
4	27/02/2023/02:00	20	0	0	15	16.09	15	65.99	8.534	7.899	17.71	
5	27/02/2023/06:00	24	1000	133.333333333333		12.67	11.55	65.99	8.534	7.899	17.71	100
6	27/02/2023/14:00	32	0	0		12.69	11.69	65.99	8.447	7.899	17.71	100

Showing 1 to 6 of 6 entries

Previous 1 Next

Case Cont.

- On the 5th day of therapy, the patient's oxygen status began to improve, and the patient began weening from the ventilator
- The patient had no episodes of over the last 24 hours
- SeCr decreased from 1.4 to 0.9 mg/dL
  - *Remember to adjust maintenance antibiotic doses!*
- The director of your unit thinks you are a genius!

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