Principles of Antibiotic Therapy

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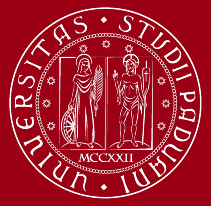
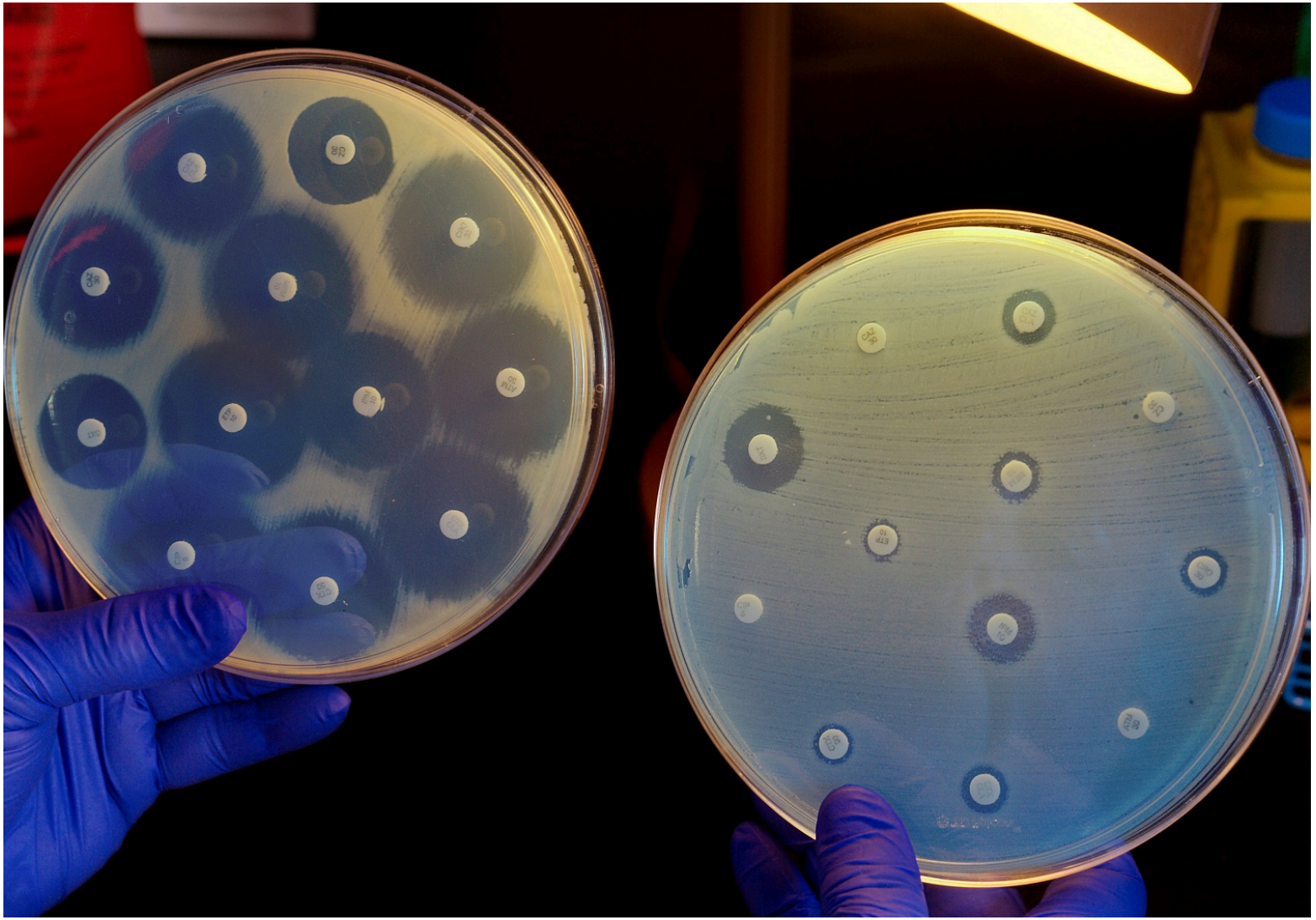
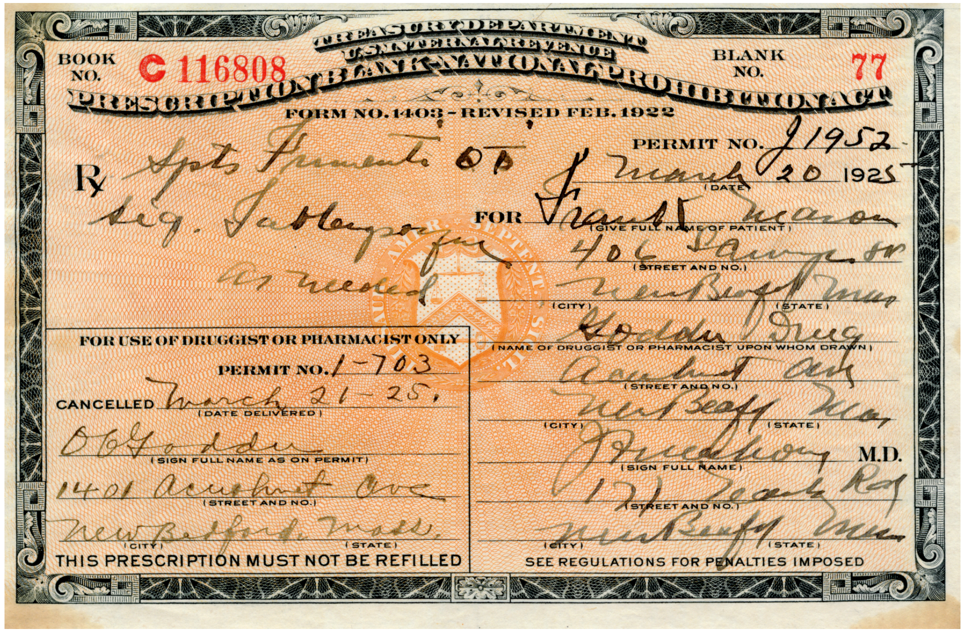


Antibiotics- The Medical Miracle



Medicine in the pre-antibiotic era



TREASURY DEPARTMENT
U.S. INTERNAL REVENUE
PRESCRIPTION BLANK NATIONAL PROHIBITION ACT

BOOK NO. C 116808

BLANK NO. 77

FORM NO. 1403 – REVISED FEB. 1922

PERMIT NO. J 1952

℞ Spts Frumenti

March 20 1925 (DATE)

FOR (GIVE FULL NAME OF PATIENT)

(STREET AND NO.)

(CITY) (STATE)

(NAME OF DRUGGIST OR PHARMACIST UPON WHOM DRAWN)

(STREET AND NO.)

(CITY) (STATE)

(SIGN FULL NAME) M.D.

(STREET AND NO.)

(CITY) (STATE)

FOR USE OF DRUGGIST OR PHARMACIST ONLY

PERMIT NO. I-703

CANCELLED March 21-25 (DATE DELIVERED)

(SIGN FULL NAME AS ON PERMIT)

(STREET AND NO.)

(CITY) (STATE)

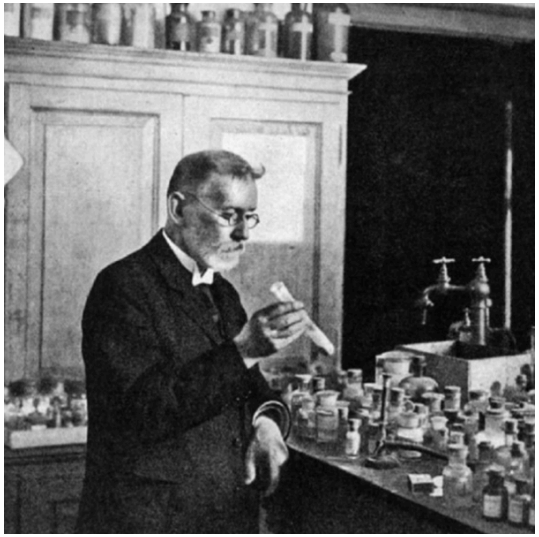
THIS PRESCRIPTION MUST NOT BE REFILLED

SEE REGULATIONS FOR PENALTIES IMPOSED

A copy of a doctor’s legal prescription for alcohol issued to a patient in Massachusetts in 1925. The doctor here wrote in a common Latin term, “spts frumenti” or spiritus frumenti, meaning whiskey

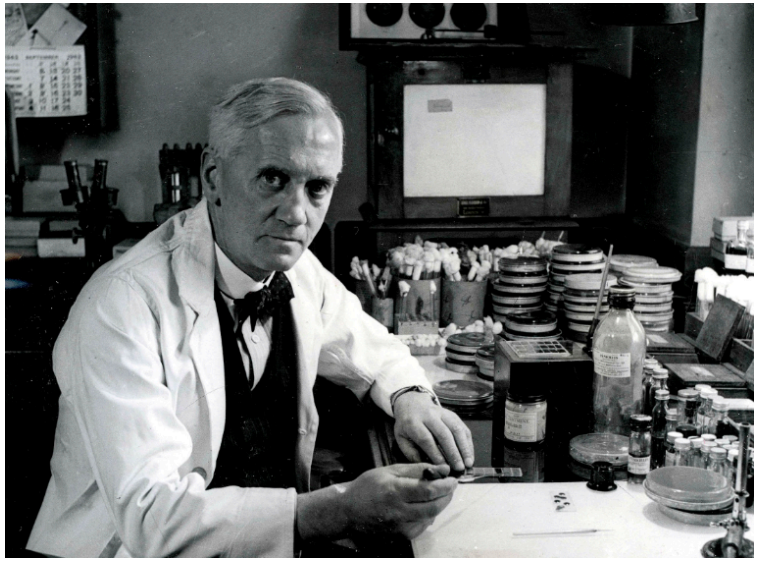
Dawn of antibiotic discovery

Paul Ehrlich, Salvarsan 1909

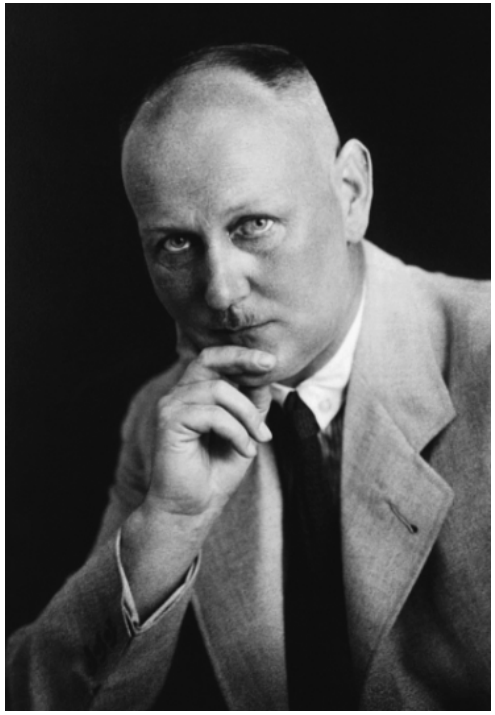


Alexander Fleming, Penicilllin 1929

Purified and tested by Florey, Chain, Heatley-1940



Gerhard Domagk, Sulfanilamides 1931



Mortality reduction with antibiotic therapy

Disease	Pre-antibiotic era	Antibiotic era	Change
Community-acquired pneumonia	~ 35%	~ 10%	-25%
Nosocomial pneumonia	~ 60%	~ 30%	-30%
Bacterial endocarditis	~ 100%	~ 25%	-75%
Gram-negative bacteremia	~ 70%	~ 10%	-60%
Bacterial meningitis	> 80%	< 20%	-60%
Cellulitis	~ 11%	< 0.5%	-10%

Antibiotics:
Essential for practice of modern medicine

- Enable complicated and deeply-invasive surgery
- Aggressive chemotherapy for cancer
- Fundamental aspects of critical care
  - e.g., central venous catheters, mechanical ventilation
- Care for premature infants, mothers (post-partum sepsis)
- Solid organ and stem cell transplantation
- **Antibiotics created a revolution in the practice of medicine, transforming a primarily diagnostic-focused field to a *therapeutic, interventional* profession**

MICROBE

Measuring Infectious Causes and Resistance Outcomes for Burden Estimation

Use this interactive visualization tool to explore our estimates for the burden of infections classified by the involved organ system (**infectious syndrome**), causative microorganism (**pathogen**), and resistance to treatment (**antimicrobial resistance**).

Key findings by location

Global

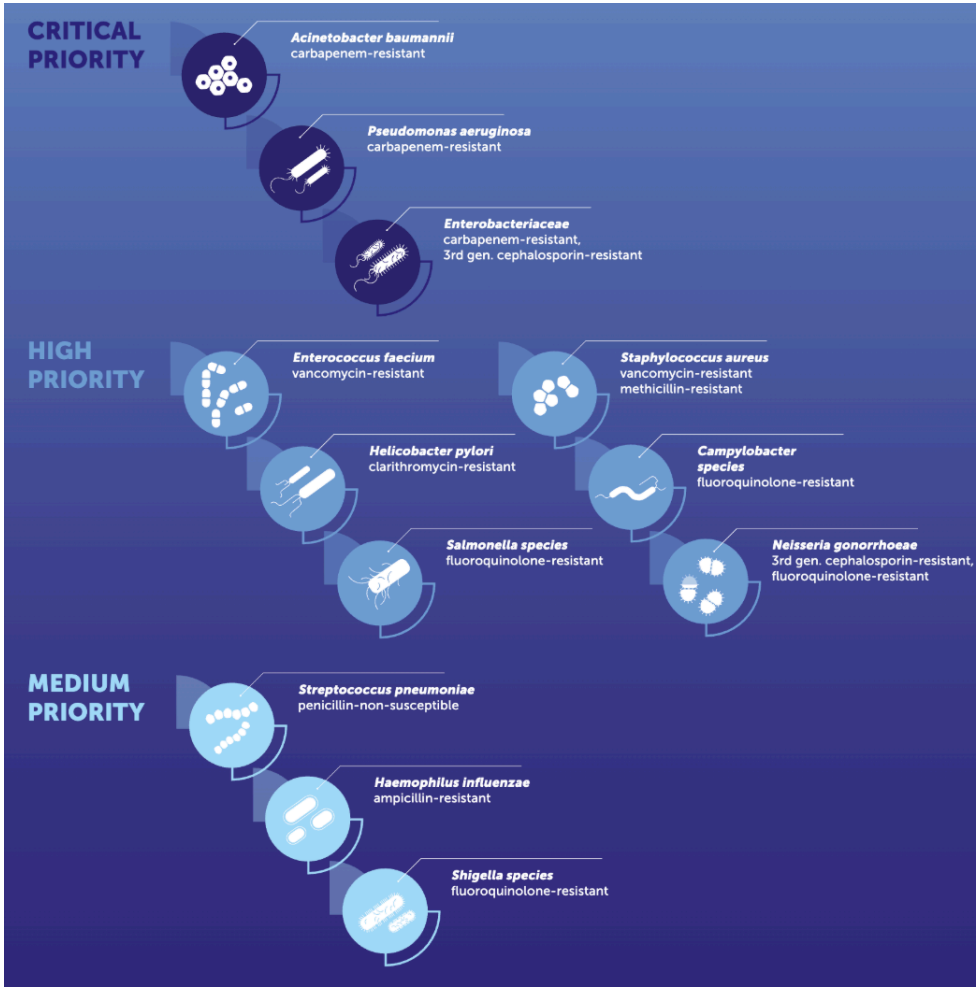
Year

2021

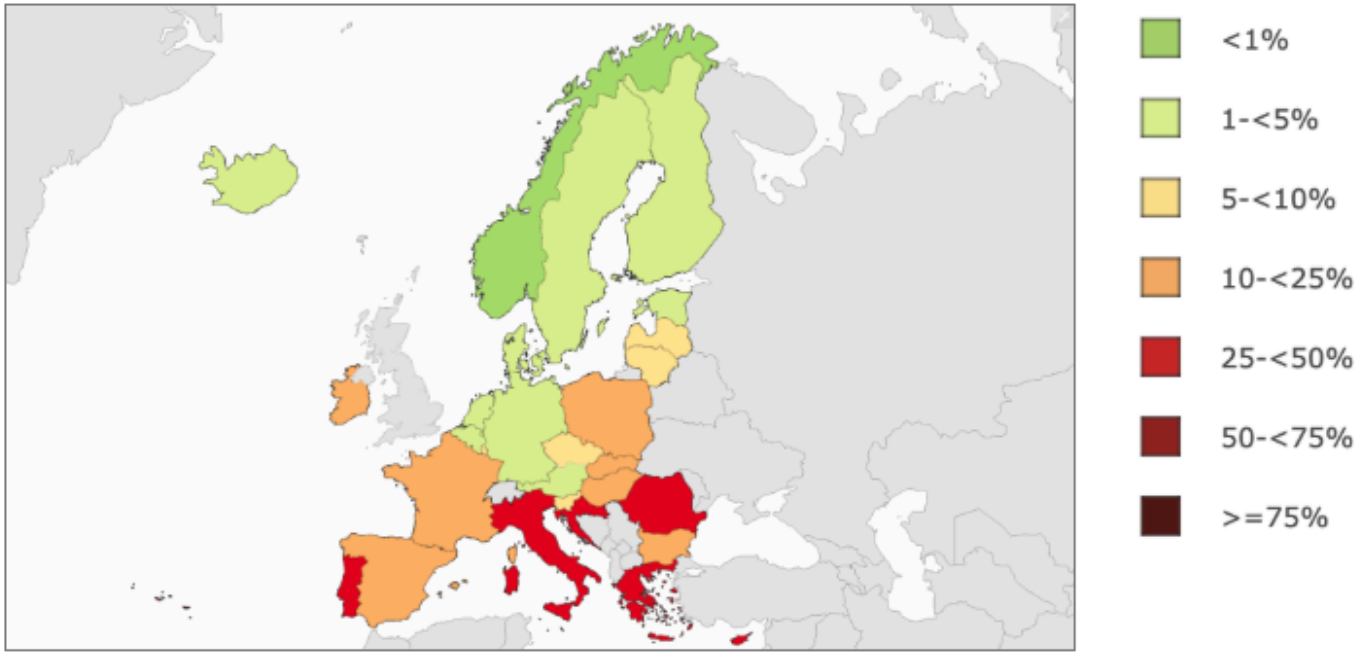
Sepsis Bacteria Resistance

Globally, between **1.14 million** and **4.71 million** people died because of **bacterial antimicrobial resistance.**

World Health Organization (WHO) Pathogen Priority List

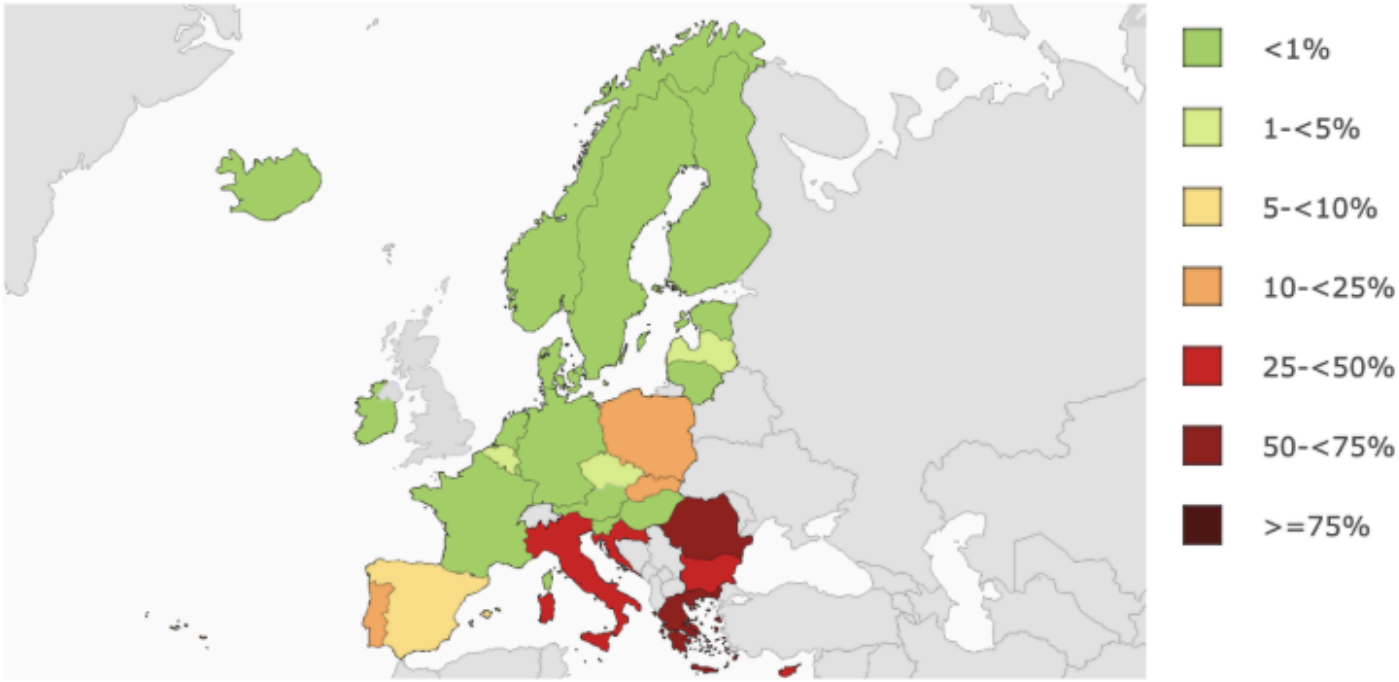


Methicillin-resistant *Staphylococcus aureus* (MRSA)



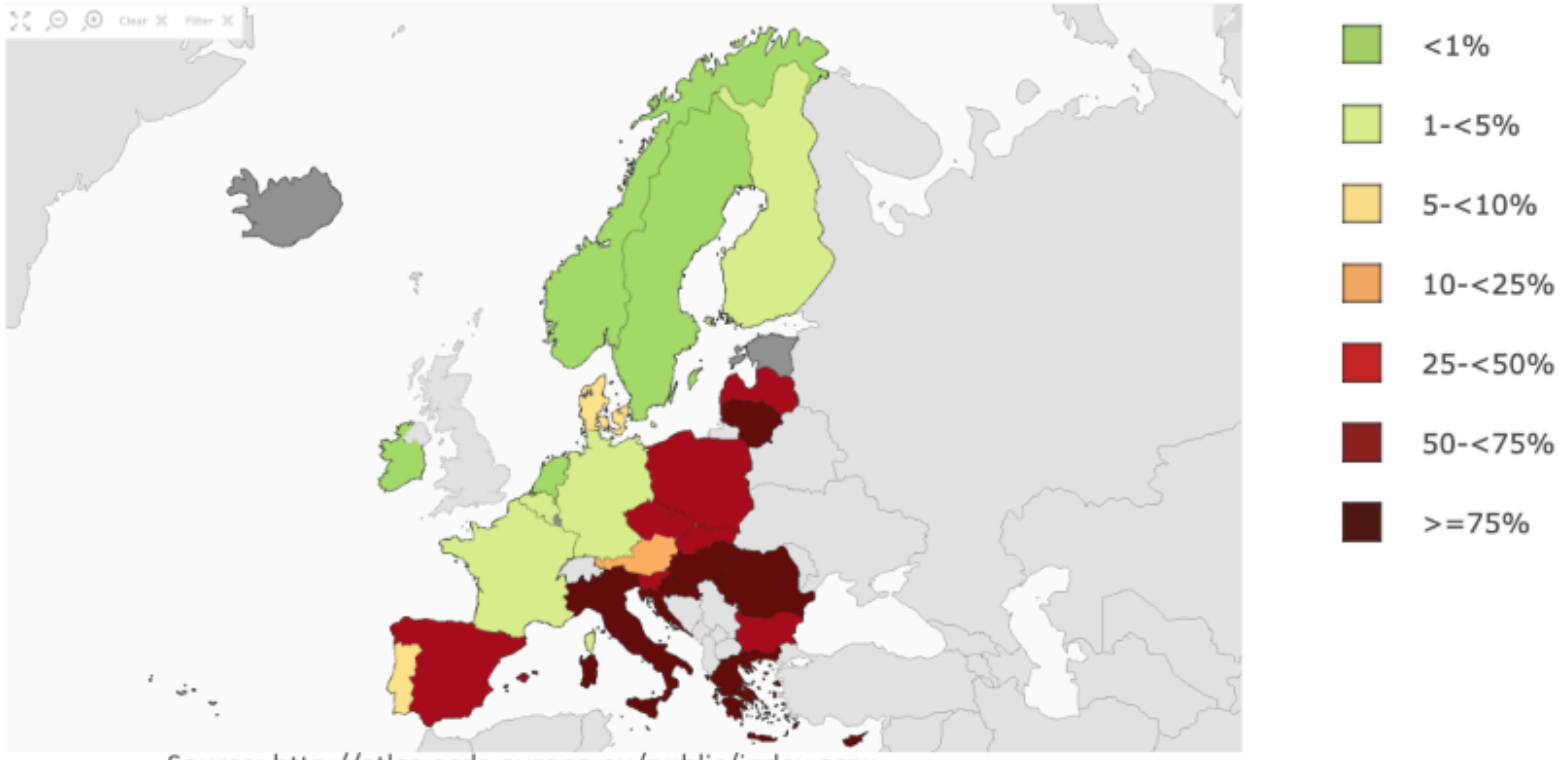
Source: http://atlas.ecdc.europa.eu/public/index.aspx

Carbapenem-resistant Enterobacterales (CRE)



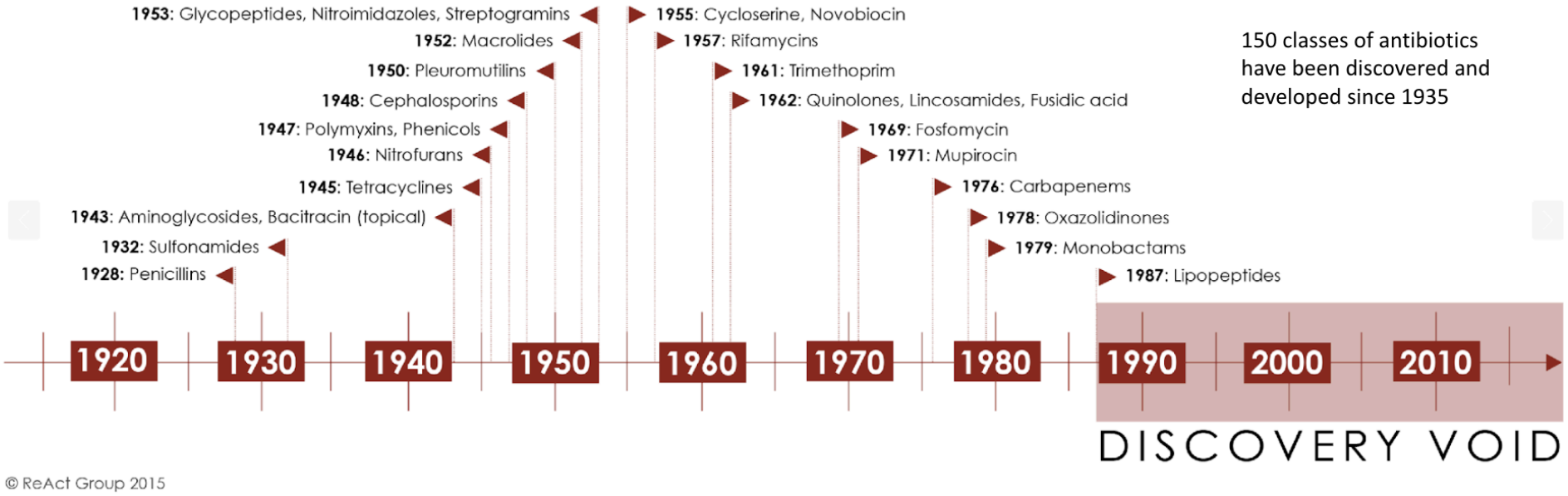
Source: http://atlas.ecdc.europa.eu/public/index.aspx

Multi-drug resistant (MDR)
Acinetobacter baumannii



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

Antibiotic discovery is slowing



150 classes of antibiotics have been discovered and developed since 1935

Antibiotics are a societal trust

- Antibiotic overprescription is a ***tragedy of the commons***: individual undertakes an action that they perceive to be in their own self-interest but that causes harm to society at large
- When such an action is undertaken rarely, the harm to society is not noticeable
- When it happens tens of millions of times per year, as with inappropriate antibiotic prescriptions, **the collective harm to society can be catastrophic**
- Given the power of antibiotics to save lives, and the constant erosion of that power through their use, **one of the most important functions of the physician is to serve as an expert** ***in the use and protection of antimicrobial agents***

Antibiotic stewardship

10 Principles for effective use of antibacterial therapy

1. Accurate differential diagnosis
2. Only use antibiotics when they alter the clinical course of disease
3. Empirically target microbes in differential diagnosis
4. A lower threshold for empirical therapy should be used in critically-ill patients
5. Host factors affect the spectrum of empirical therapy
6. Use PK/PD principles to select and optimally dose treatment
7. De-escalate antibiotic therapy based on microbiology results and clinical (biomarker) responses
8. If therapy is not working, consider source control or alternative diagnosis before broadening therapy
9. Distiniguish new infection from failure of initial therapy
10. The duration of therapy should be as short as possible based on available evidence (shorter is better)

Principle #1: Develop an accurate differential diagnosis

What is the most important component in diagnosing infectious diseases?

A. Patient medical history

B. Physical exam

C. Radiological imaging (e.g., X-ray, CT or MRI)

D. Biomarkers of infections (e.g., c-reactive protein, procalcitonin)

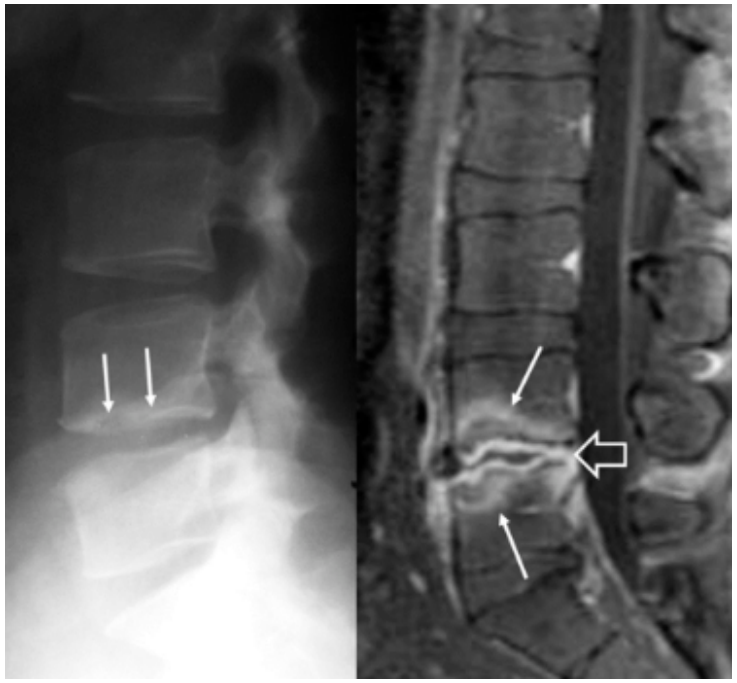
E. Microbiological tests (e.g., culture, PCR, serology)

Medical history is 80% of diagnosis in infectious diseases

- **What are the current symptoms** (e.g., fever, pain, cough, breathlessness, confusion, lethargy, vomiting, and any acute or subacute changes in functional status such as new urinary incontinence, falls, or decreased oral intake)
  - **8 cardinal descriptors**: Timing, Location, Character, Aggravating Factors, Alleviating Factors, Associated Symptoms, Severity, Setting
- **Fever** How high, how long, what pattern?
- **Risk factors for infection** (e.g., indwelling devices -urinary catheters, vascular catheters, prosthetic joints, cardiac devices), recent medical procedures, immunosuppression, diabetes, history of injection drug use, and previous infections
- **Travel or exposure history** (e.g., recent travel -countries, regions, urban/rural, dates, exposure to animals or insect bites, contact with ill individuals, and consumption of potentially contaminated food or water)
- **Sexual history** and risk for sexually transmitted infections
- **Vaccination history**
- **What is the past medical and surgical history, medication use, and allergies?**
- **Are there any recent changes in medications or antibiotic use?**
- **What is the social history?** (e.g., living situation (e.g., long-term care facility), occupation, hobbies, and substance use, which may affect exposure risk)

Case Example

- **Chief complaint:** 34 year-old farmer from Sicily presents with worsening back pain after sitting for more than couple of hours
- **No other significant past medical history**
- **Spondylitis etiologies:**
  - > 50% *Staphylococcus aureus, Staphylococcus epidermidis*
  - ~ 25% *Streptococcus* spp., *Enterococcus* spp. *Pseudomonas aeruginosa, Enterobacter* spp., *Proteus* spp. *E. coli*, *Serratia* spp., Anaerobes, *Mycobacterium tuberculosis* (Pott's disease)

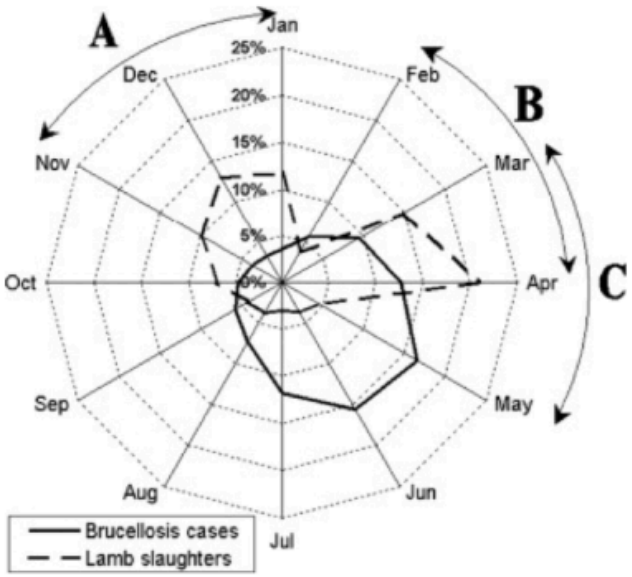


Initial lateral radiograph (left) shows a cortical disruption at the inferior epiphyseal plate of L4 vertebral body (arrows). The sagittal fat suppressed contrast enhanced T1-w MR image (right) shows septic discitis (open arrow) and bone marrow edema on both L4 and L5 vertebral bodies (arrows), suggesting spondylitis.

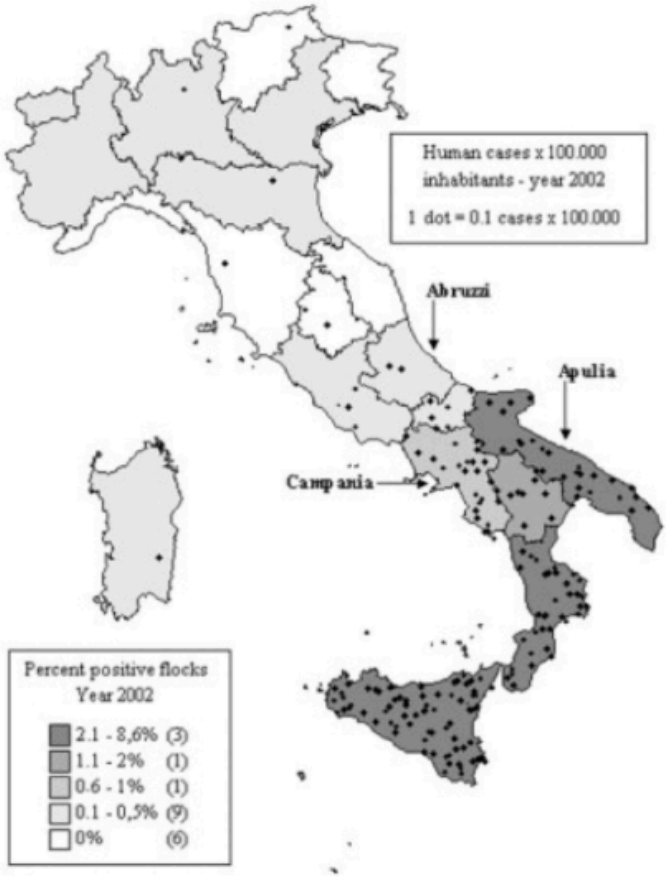
Pertinent history!

- Patient works as a sheep and cattle farmer in a small enterprise 54 minutes from Messina that produces milk and cheese: Percorino salato and Ricotta
- Patient reported pain was first noticed at end of May after a bad case of flu “fever, achy joints, headache”
- Father (who also works on farm) also has worsening hip pain after sitting for long periods and will be evaluated by an orthopedic doctor for hip replacement.
- Other 3 brothers and cousin who work on farm report no illness.

Could this be brucellosis?



- Calculated occupational exposure risk of 25%
- Peak between April and June
- Temporal correlations suggest many infections are related to the production and consumption of fresh cheese



Zoonotic Gram-negative coccobacilli

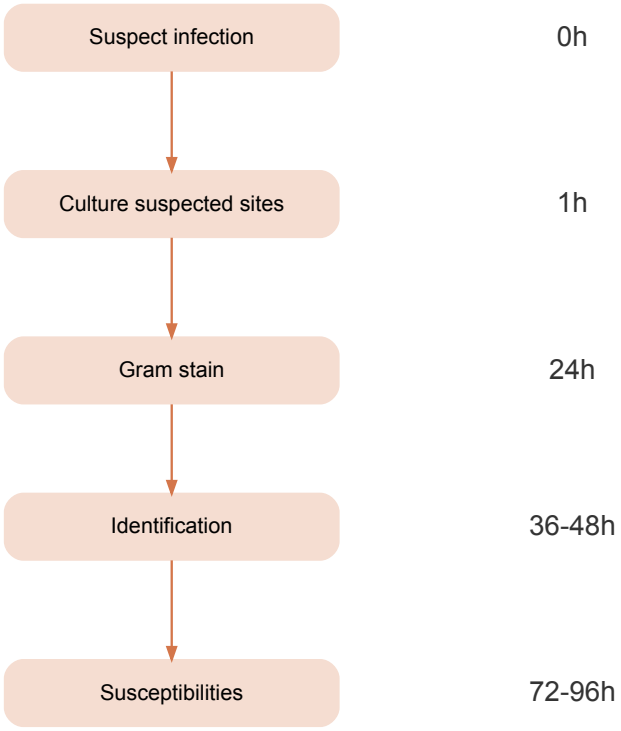
Diagnosis and treatment of Brucellosis spondylitis:

Specialized diagnostics and therapy!

- Blood cultures require special procedures (prolonged incubation), bone culture may be needed
- Brucella PCR from clinical specimen
- Combination serologic studies
- Treatment- Gentamicin + Doxycycline + Rifampin
  - Unconventional antibiotic regimen, would not be covered by standard spondylitis regimens

Antibiotics are usually started empirically

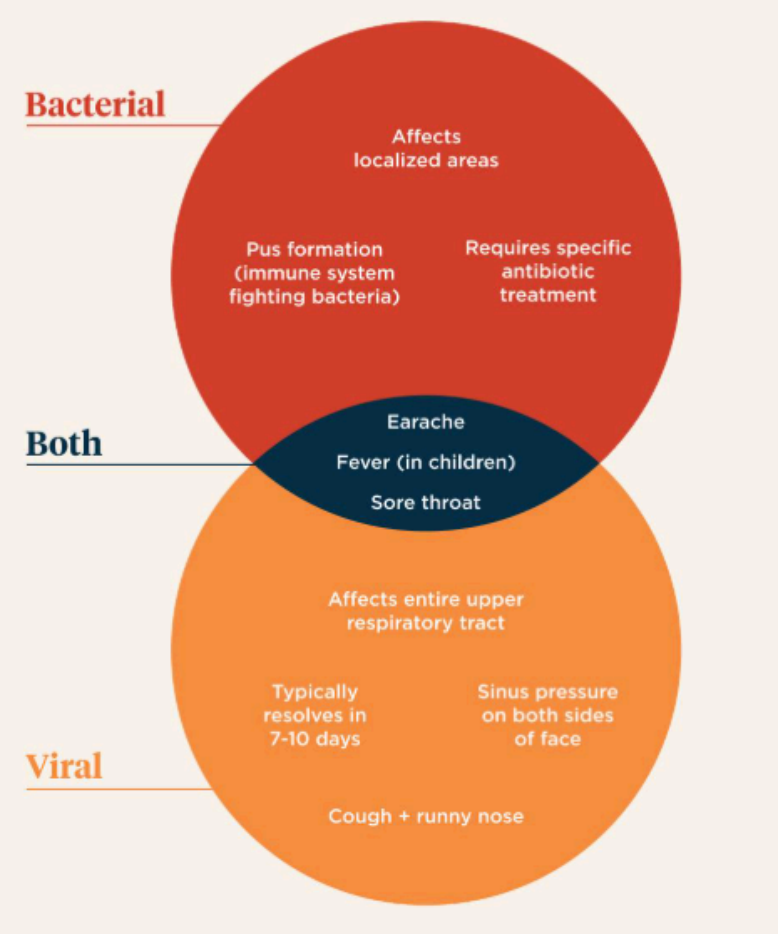
Begin **empiric therapy** for likely pathogens



Change to **definitive therapy** for patient-specific pathogens

Antibiotics are usually started empirically

Antibiotics should only be started if the differential diagnosis includes likely invasive bacterial infections:
90-98% of upper respiratory tract infections are caused by viruses



Clinicians frequently *overestimate* the risk of bacterial infection

Doctors frequently *underestimate* the risks of antibiotic therapy

⚠ **1 in 5 patients given antibiotic prescriptions are harmed by them because of adverse events or superinfection by resistant pathogens or *Clostridioides difficile***

⚠ **Every additional 10 days of antibiotic therapy confers a 3% increased risk of an adverse drug effect**

A combination of:

- Fear from uncertainty of the diagnosis
- Lack of appreciation of how dangerous antibiotics can be

Association of adverse events with antibiotic use in hospitalized patients

Table 3. Proportion of 30-Day Antibiotic-Associated Adverse Drug Events in 1488 Hospitalized Patients Receiving Systemic Antibiotic Therapy[a]

Antibiotic Agent	No. of Patients Receiving Agent	No. (%)						
		Cardiac	Gastro-intestinal[b]	Hematologic	Hepato-biliary	Renal	Neurologic	Other Events[c]
β-Lactams[d]	1187	0	59 (5.0)	27 (2.3)	6 (0.5)	17 (1.4)	10 (0.8)	2 (0.2)
Ampicillin	63	0	2 (3.2)	1 (1.6)	1 (1.6)	1 (1.6)	0	0
Amoxicillin-clavulanate	102	0	3 (2.9)	0	0	0	0	0
Ampicillin-sulbactam	52	0	1 (1.9)	0	0	2 (3.8)	0	0
Oxacillin	33	0	4 (12.1)	1 (3.0)	2 (6.0)	0	0	0
Piperacillin-tazobactam	315	0	16 (5.1)	4 (1.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Cefazolin	79	0	0	1 (1.3)	0	2 (2.5)	0	0
Ceftriaxone	607	0	14 (2.3)	11 (1.8)	3 (0.5)	5 (0.8)	1 (0.2)	0
Cefpodoxime	89	0	2 (2.2)	0	0	0	0	0
Cefepime	414	0	10 (2.4)	6 (1.4)	0	6 (1.4)	7 (1.7)	1 (0.2)
Ertapenem	85	0	3 (3.5)	0	0	0	0	0
Meropenem	80	0	4 (5.0)	3 (3.8)	0	0	1 (1.3)	0
Non-β-lactams								
Aminoglycosides	32	0	0	0	0	2 (6.3)	0	0
Azithromycin	400	1 (0.3)	1 (0.3)	0	4 (1.0)	0	0	0
Clindamycin	193	0	3 (1.6)	0	0	0	0	0
Daptomycin	8	0	0	0	0	0	0	1 (12.5)
Doxycycline	57	0	2 (3.5)	0	0	0	0	0
Fluoroquinolones	394	1 (0.3)	5 (1.3)	1 (0.3)	3 (0.8)	1 (0.3)	1 (0.3)	1 (0.3)
Linezolid	23	0	0	0	0	0	1 (4.3)	0
Metronidazole	175	0	1 (0.6)	0	0	0	1 (0.6)	0
Trimethoprim-sulfamethoxazole	155	0	5 (3.2)	0	0	6 (3.9)	0	1 (0.6)
Intravenous vancomycin	544	0	2 (0.4)	0	0	19 (3.5)	0	2 (0.4)
Any antibiotics	1488[e]	2 (0.1)	78 (5.2)	28 (1.9)	13 (0.9)	45 (3.0)	13 (0.9)	7 (0.5)

[a] The following regimens are included in the overall rates and resulted in no 30-d adverse drug events: penicillin (21), amoxicillin (47), dicloxacillin (1), cephalexin (44), second-generation cephalosporins (38), ceftazidime (6), ceftaroline (8), aztreonam (22), fosfomycin (10), nitrofurantoin (26), tigecycline (3), oral vancomycin (84).

[b] Includes nausea, emesis, non-*Clostridium difficile*–associated diarrhea.

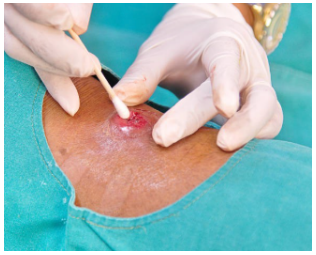
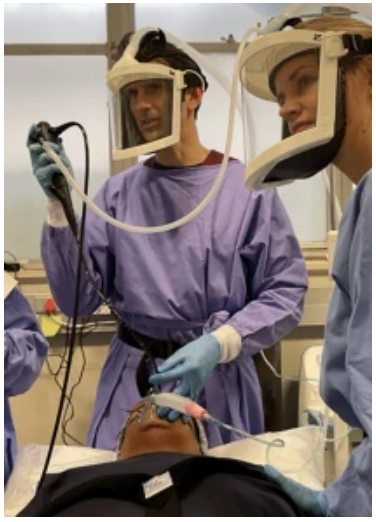
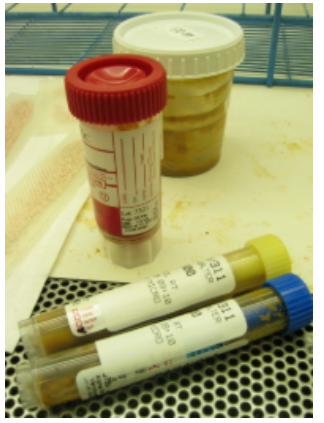
[c] Other adverse drug events include cefepime-associated anaphylaxis (1), piperacillin-tazobactam–associated drug fever (1), ciprofloxacin-associated tendinitis (1), daptomycin-associated myositis (1), trimethoprim-sulfamethoxazole–associated pancreatitis (1), vancomycin-associated hives (1), and trimethoprim-sulfamethoxazole-associated nonhives rash (1).

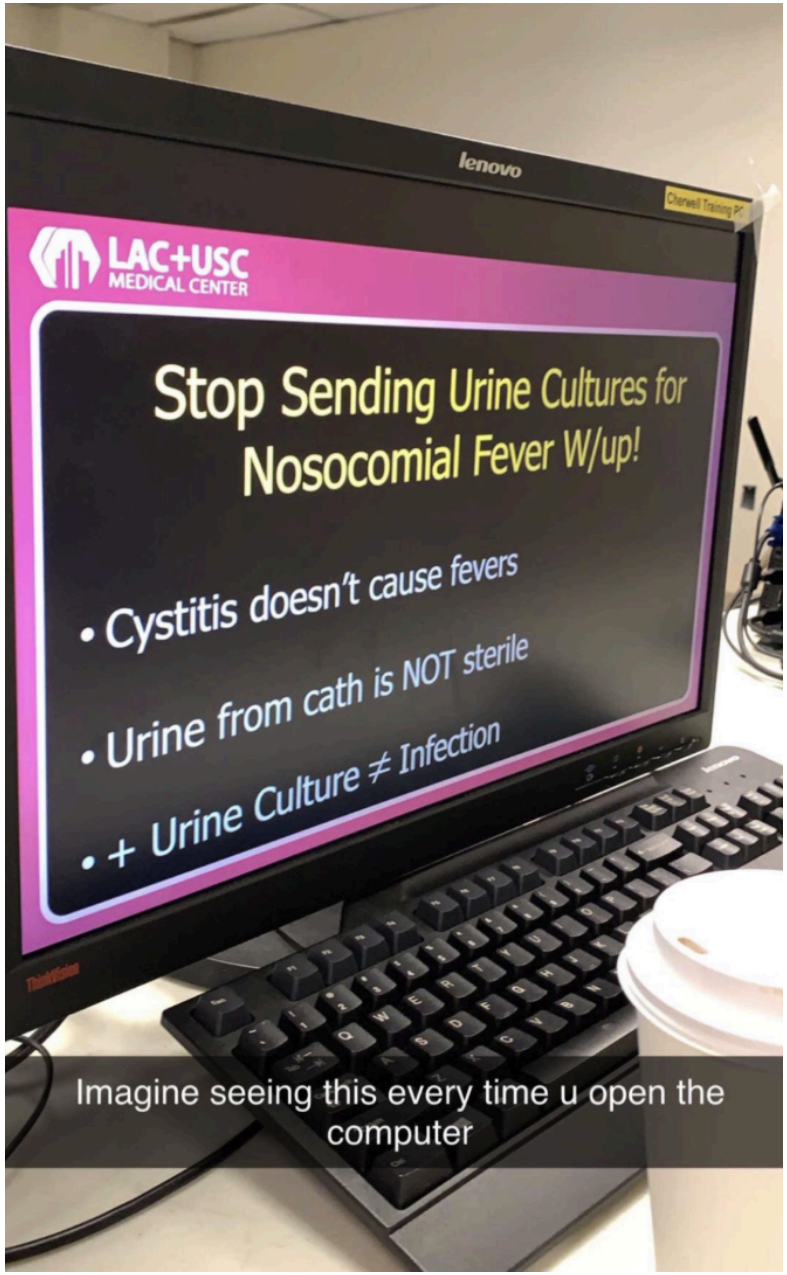
[d] Some patients received more than 1 β-lactam antibiotic.

[e] Most patients (1176 [79%]) received more than 1 antibiotic.

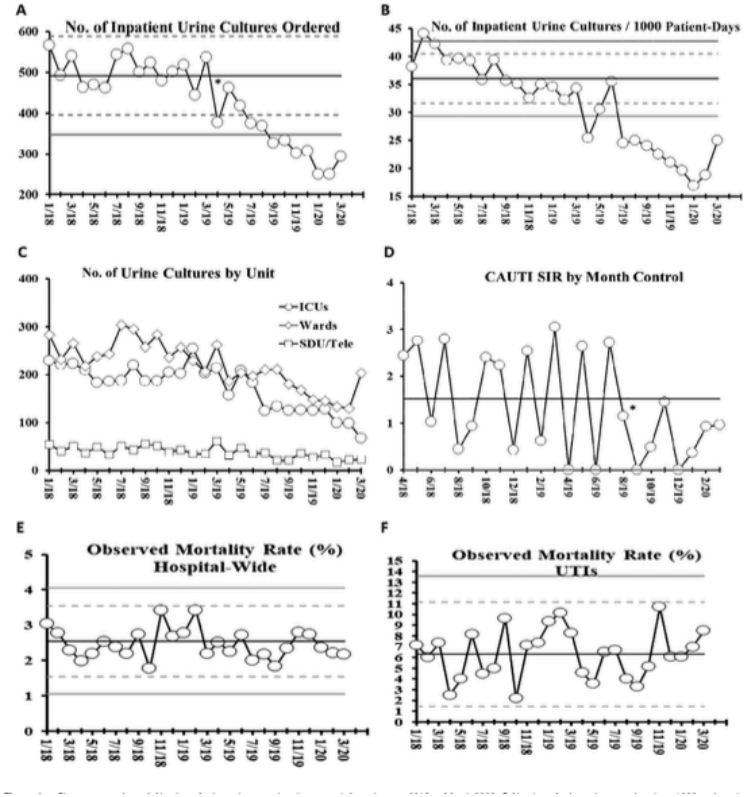
Positive cultures are not always proof of infection

- The presence of a positive culture in the absence of signs or symptoms of infection **should not** reflexively trigger antibiotic prescription
- Without symptoms, a positive culture often represents **colonization or contamination and should not necessarily trigger treatment**

Wound swabs	Urine cultures	Bronchial alveolar lavage	Respiratory samples	GI tract/stool
				


lenovo
LAC+USC
MEDICAL CENTER
Stop Sending Urine Cultures for Nosocomial Fever W/up!
• Cystitis doesn't cause fevers
• Urine from cath is NOT sterile
• + Urine Culture ≠ Infection
Imagine seeing this every time u open the computer

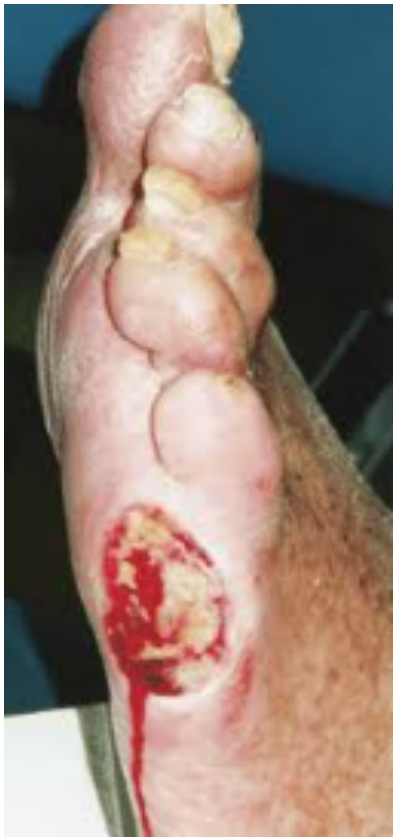
Simple stewardship intervention



Principle #2: Only use antibiotics when they alter the clinical course of patients

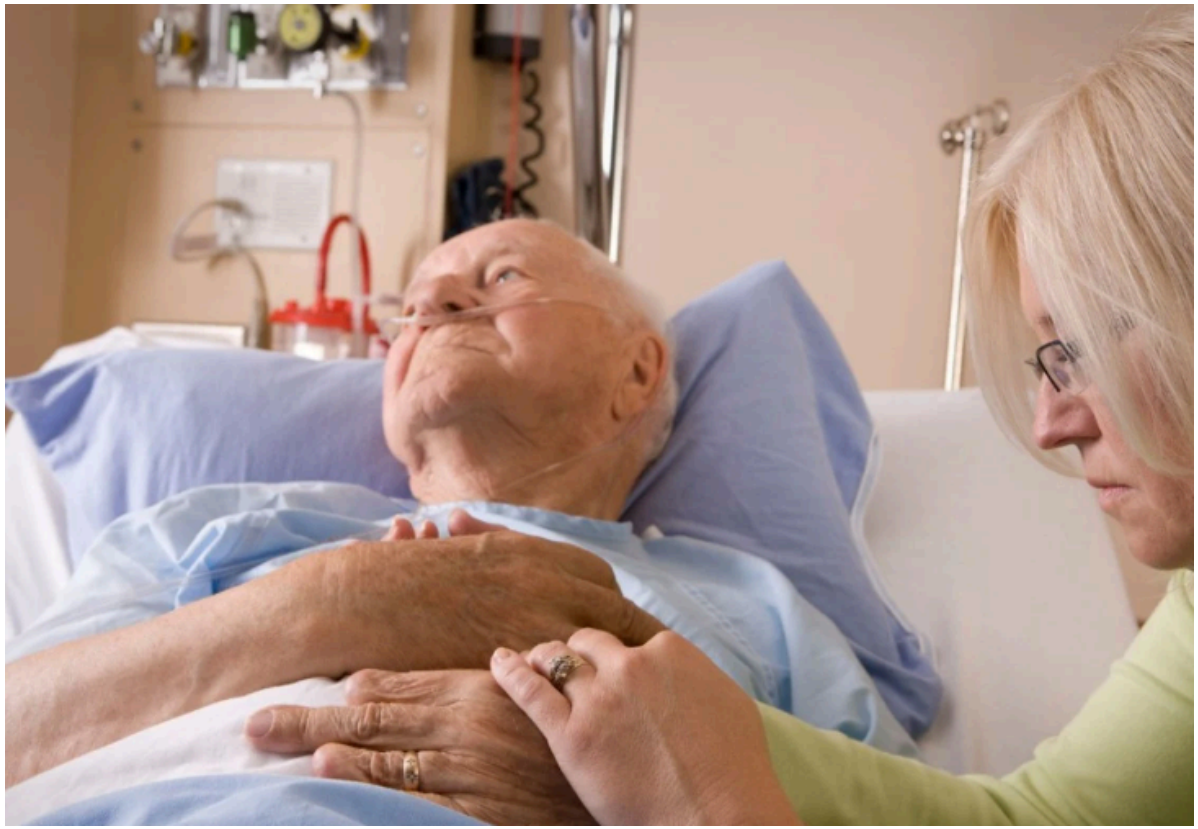
Antibiotics are not the only answer

- The administration of antibiotics should not be a reflexive response to infection, but should be incorporated into an overall, rational therapeutic plan for the patient.
- Patients who lack bacterial infections cannot have their clinical course improved by antibiotics (as discussed in Principle #1).



Ethical dilemmas for use of antimicrobial therapy

End of life (comfort care)

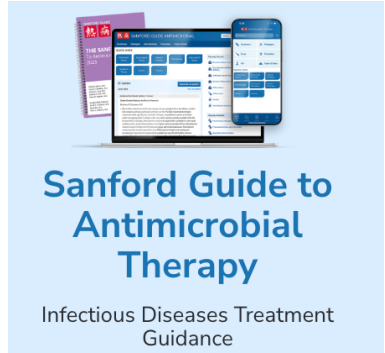


Non-adherent HIV therapy

Principle #3: Empirically target microbes in differential diagnosis

Know the spectrum of activity

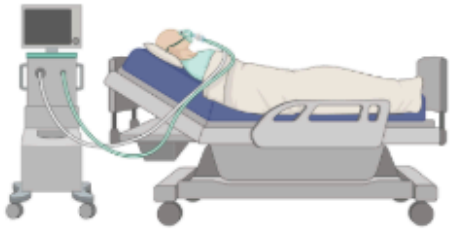
- Spectrum of activity of the empirical antiinfective agents prescribed should be tailored to cover the likely microbial flora that cause the diseases in the differential diagnosis



Sanford Guide

Community-acquired vs. nosocomial

Lower respiratory tract infection



Community-acquired

- Viral (influenzae, Sars CoV-2)
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- Atypical bacteria
  - (e.g., Mycobacteria, Chlamydia, Legionella)

Hospital-acquired

- Gram negatives, including possibility of MDR isolates (*K. pneumoniae, E. coli*)
- Non-fermenting Gram-negatives, including MDR (*P. aeruginosa, Acinetobacter baumannii*)
- Methicillin-resistant Staphylococcus aureus (MRSA)

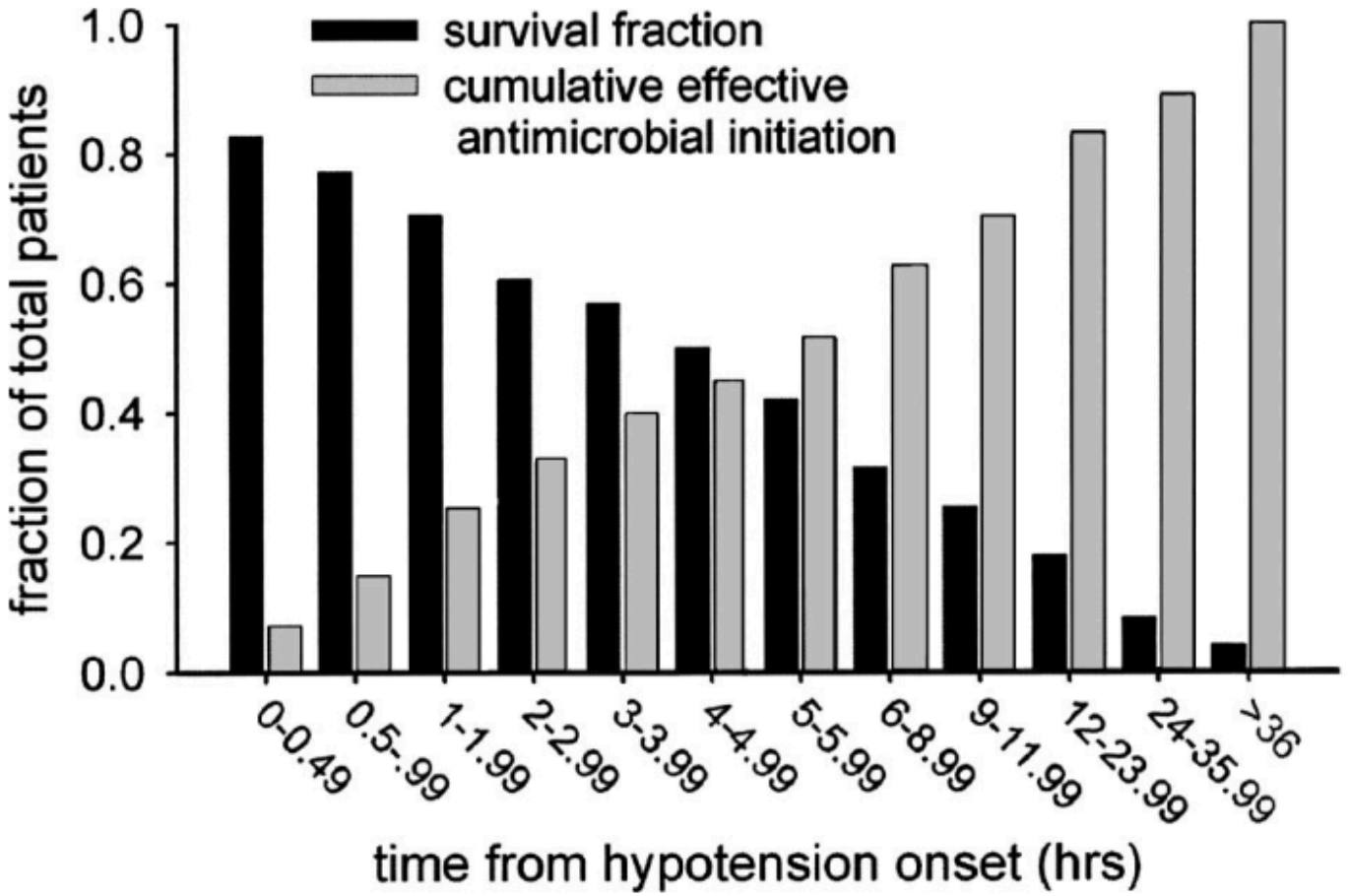
Basic principles of coverage

Community infections	Nosocomial infections
• Community-associated infections are infrequently caused by MDR gram-negative bacteria. • Empirical antibiotic coverage should not routinely considered	• More often caused by more resistant pathogens, and hence require coverage for P*seudomonas* or other non-fermenting gram-negative bacilli
Avoid using routine methicillin-resistant *S. aureus* (MRSA) empirical therapy in patients who are unlikely to be infected with MRSA	Greater risk for MRSA, especially is patient has recently received antibiotic therapy
Reserve the use of antimicrobials that can be used as last-line oral therapeutic options (e.g., fluoroquinolones) for infections for which there are no reasonable alternative therapies	May require "frontline" used of lastline antibiotic if patient has risk factors for multidrug resistant infection

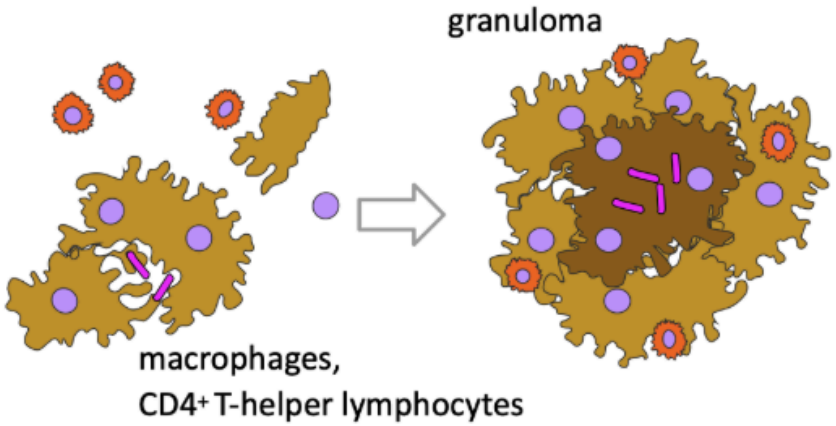
Special circumstances creates exceptions: For example, community-acquired pneumonia and intraabdominal, skin, and urinary infections may be caused by Pseudomonas in patients with cystic fibrosis or with history of bronchiectasis, chronic dialysis patient, or patient with indwelling catheters or recent surgery.

Principle #4: There is a lower threshold for empirical therapy in critically-ill patients

Antibiotic timing is critical in septic shock



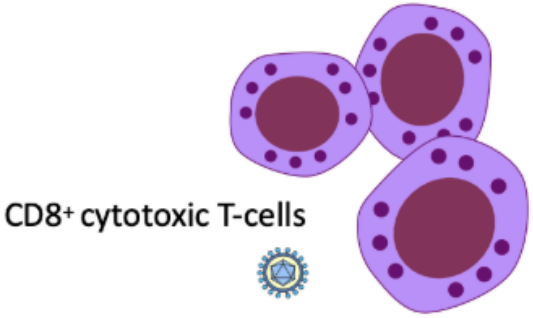
Principle #5: Host factors affect the spectrum of empirical therapy



Intracellular bacteria...
Mycobacterium tuberculosis
Atypical mycobacterium
Legionella spp.
Listeria monocytogenes
Salmonella typhi
Nocardia spp.

Fungi...
Candida spp.
Endemic fungi
Cryptococcus neoformans
P. jiroveci

Parasites...
Toxoplasma gondii
Cryptosporidium
Leishmania



Viruses...
Herpes simplex
Varicella zoster
Cytomegalovirus
HHV-6
Epstein-Barr

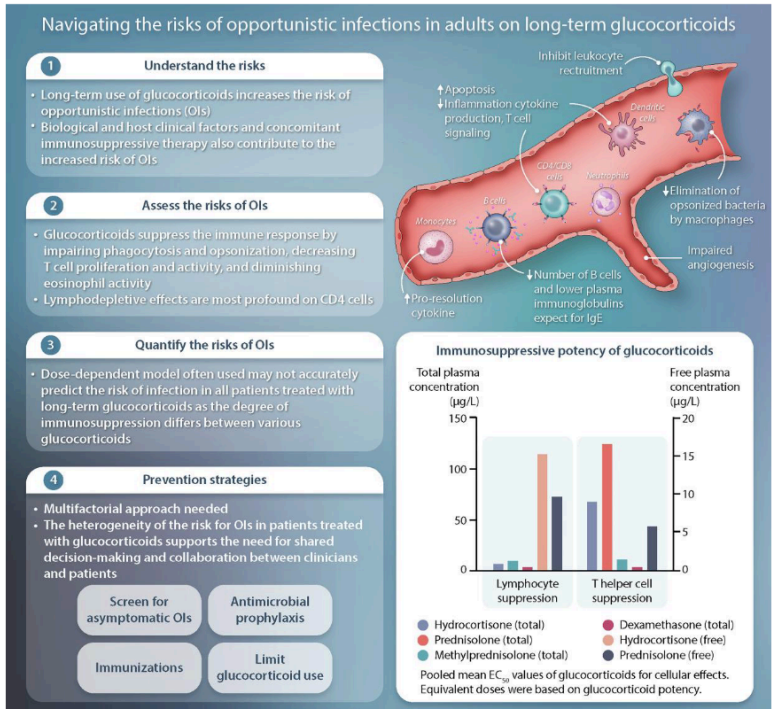
Adenovirus
Polyomaviruses
Influenza
Parainfluenzae
RSV

Examples of common predisposing conditions-drugs: AIDS, allogeneic HSCT, high-dose corticosteroids, purine analogue chemotherapy (fludarabine), polyclonal and monoclonal T-cell depleting antibodies, temozolamide, T-cell depleting antibodies (alemtuzumab)

Common immunocompromised conditions

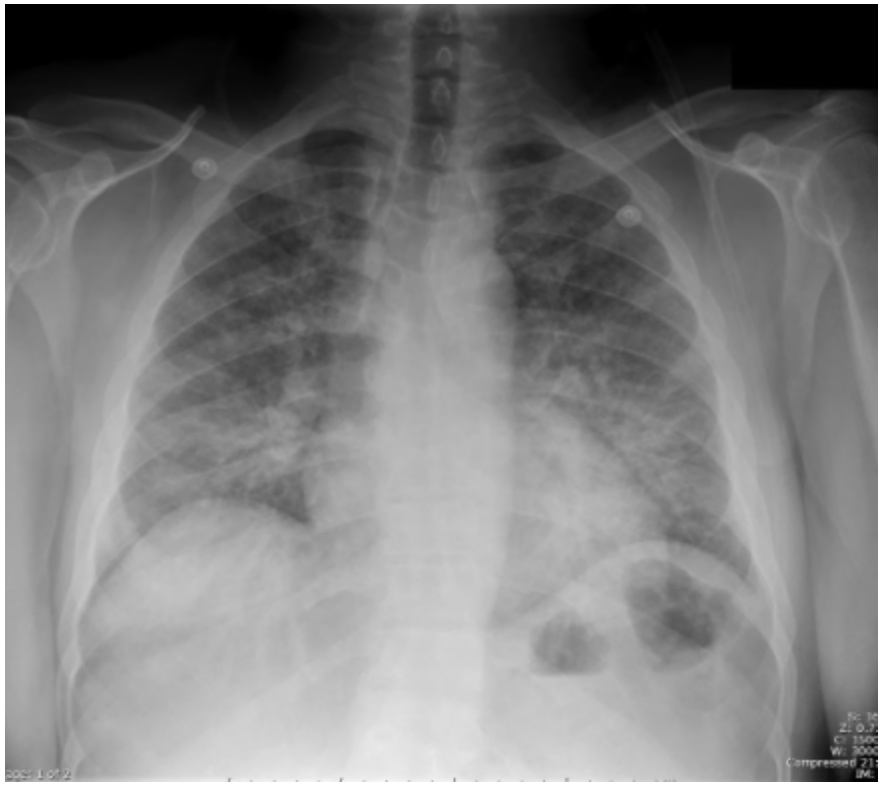
1. Chronic diseases (e.g., type 1 diabetes, chronic obstructive pulmonary disease)
2. Autoimmune diseases (e.g., lupus, rheumatoid arthritis)
3. Genetic diseases (primary immunodeficiencies)
4. Cancer and/or chemotherapy
5. Human immunodeficiency virus (HIV)
6. Solid organ or bone marrow transplant
7. Advanced age
8. Malnutrition
9. **Chronic use of corticosteroids or other immunosuppressive medications**
10. Chronic infections
11. Smoking

Glucocorticoids: "Credit cards" of immunosuppressive therapy

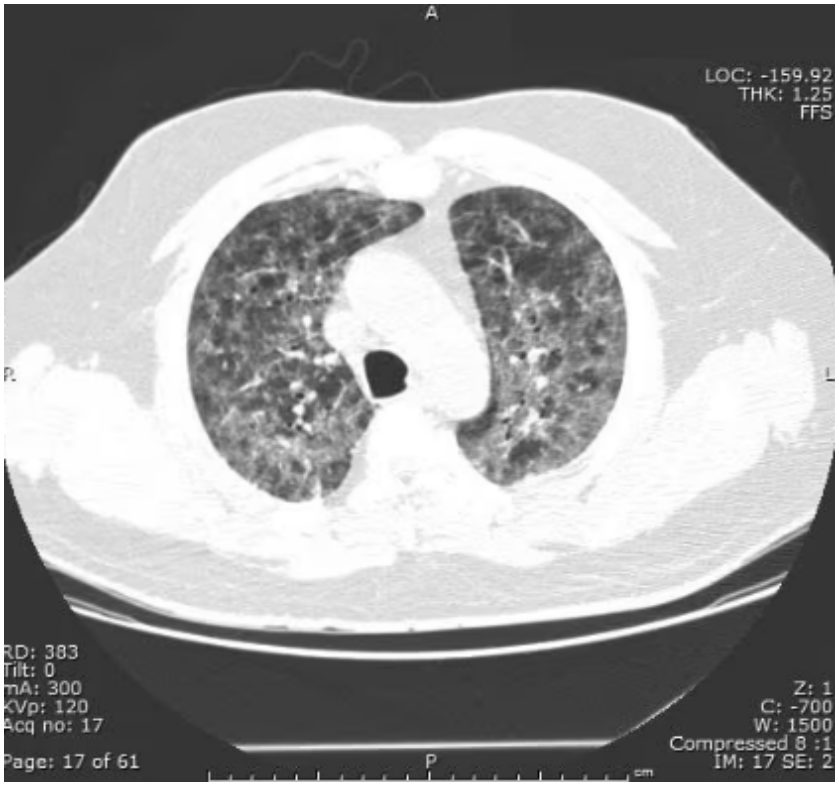


Dose-dependent increase in the risk of opportunistic infections > 10 mg of prednisone equivalents (PEQ) per day for 2-4 weeks

Community acquired pneumonia (CAP) vs. Pneumocystis jirovecii pneumonia (PCP)

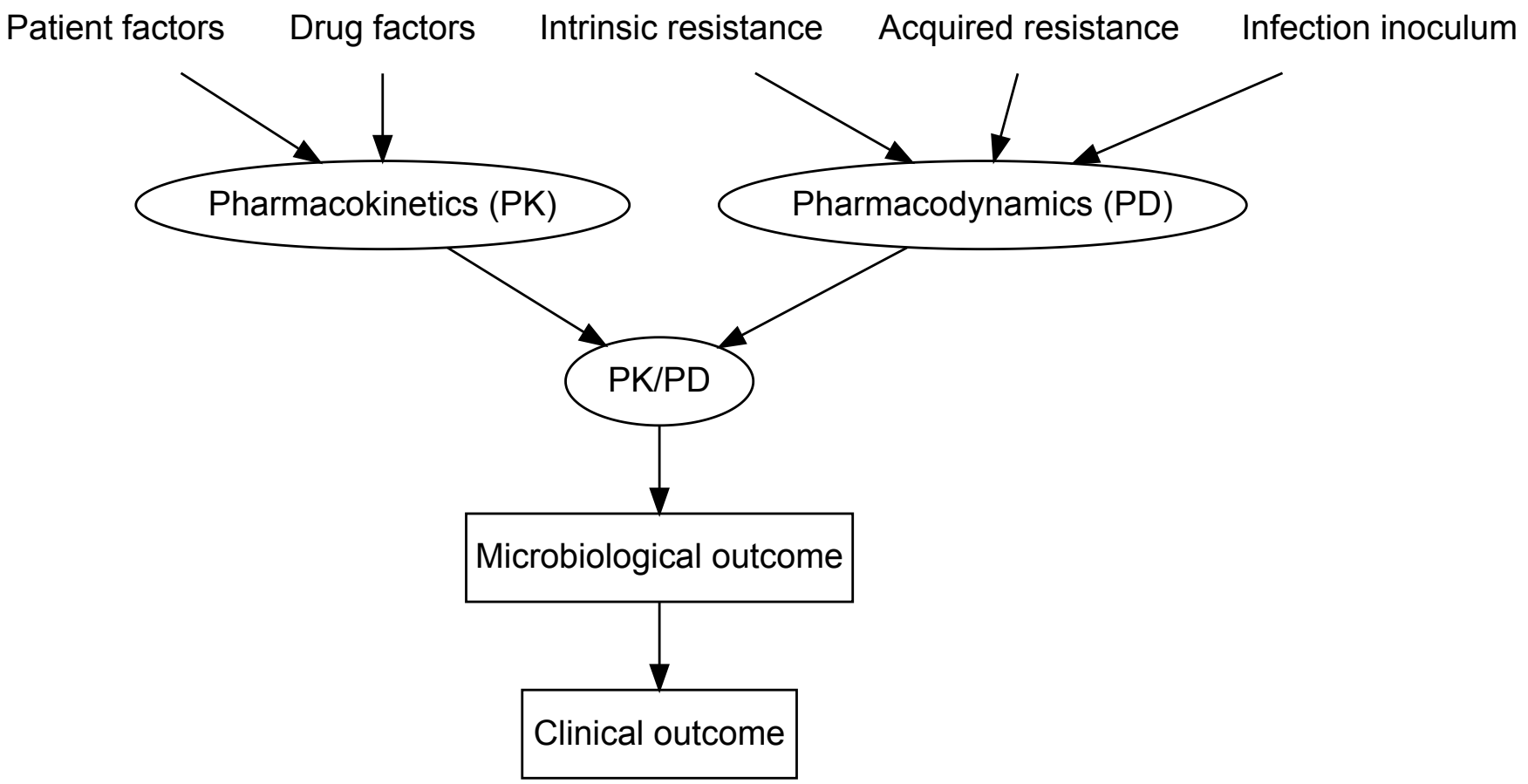


Diffuse bilateral infiltrates

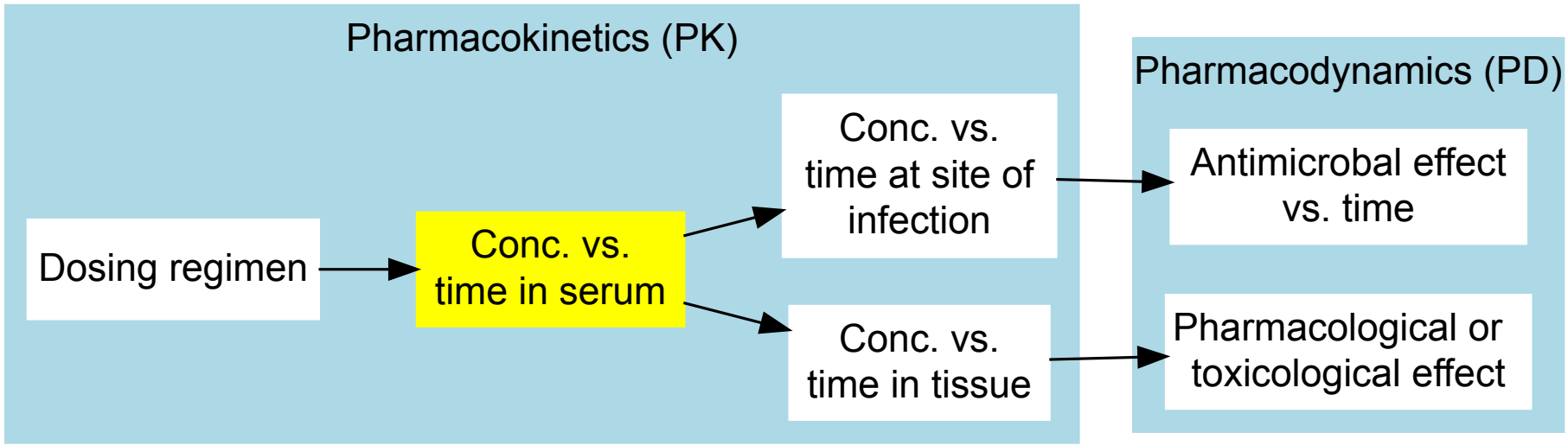


Patchy areas of ground-glass attenuation

Principle #6: Use PK/PD principles to optimize treatment selection and dosing

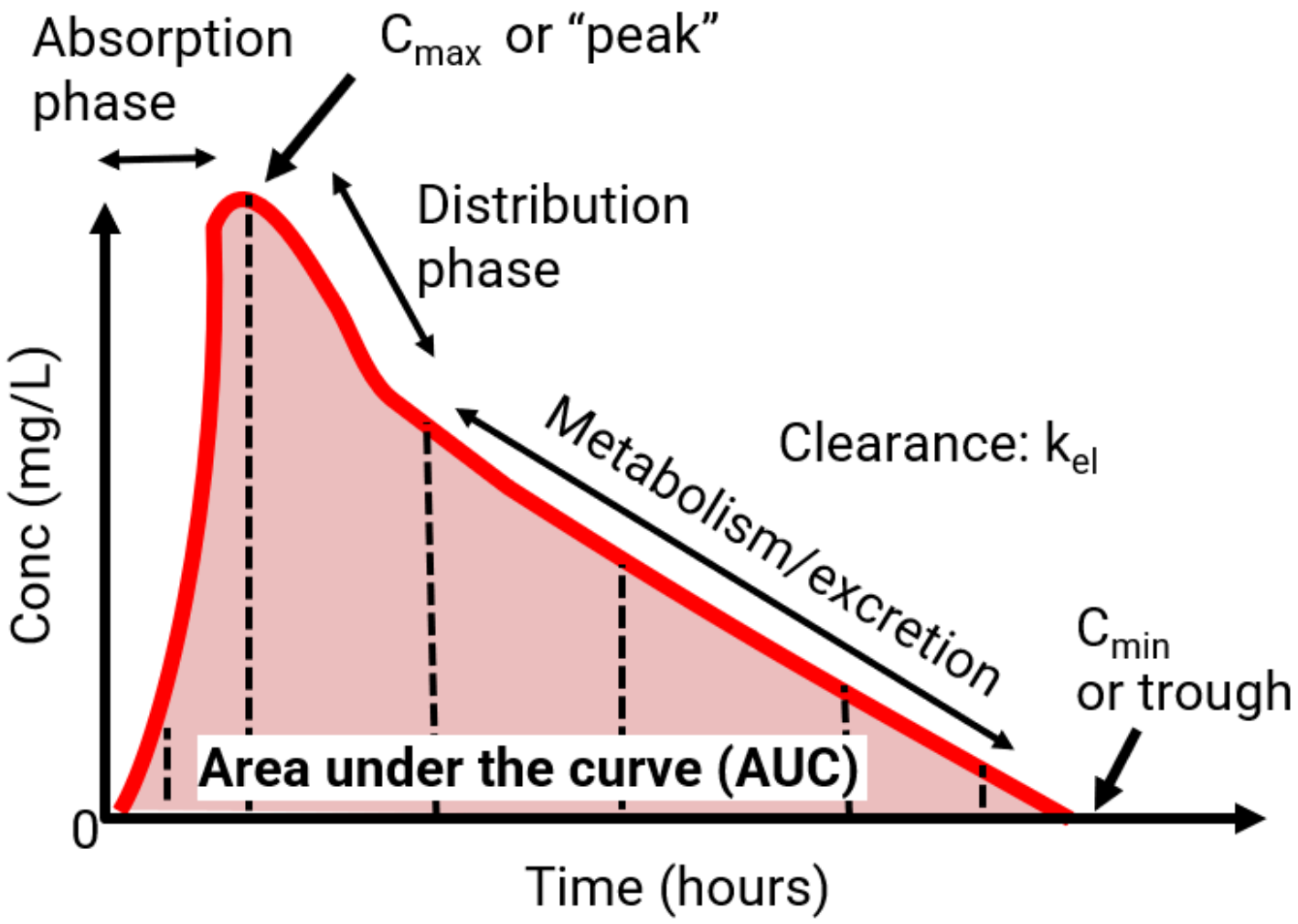


Pharmacology of antimicrobials



Absorption
Distribution
Metabolism
Elimination

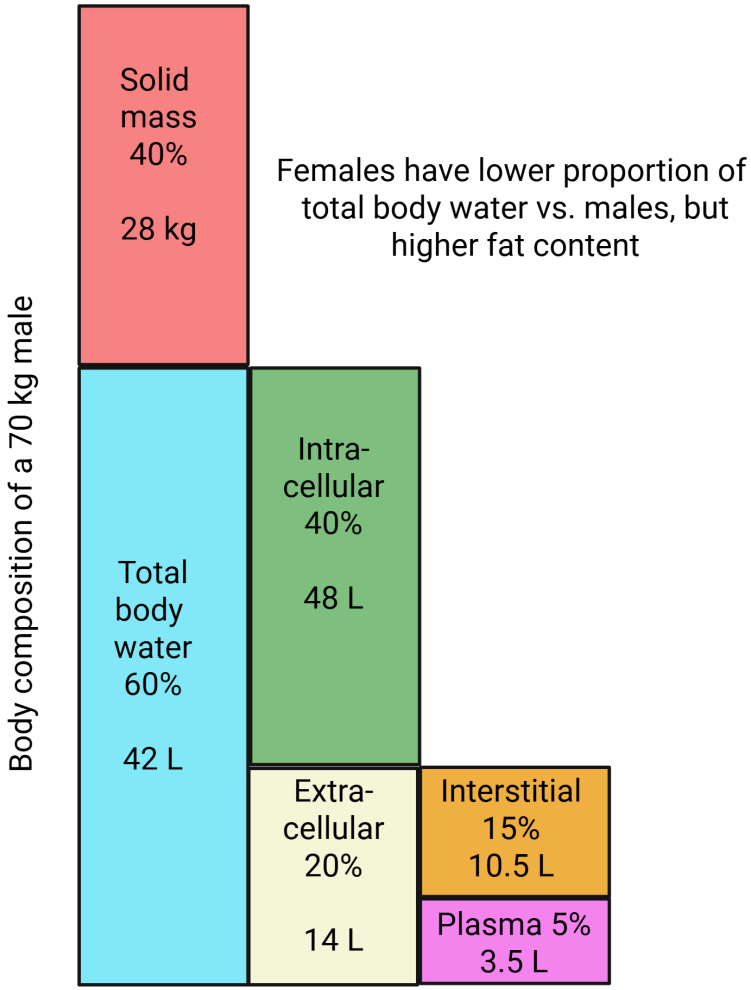
Key pharmacokinetic variables



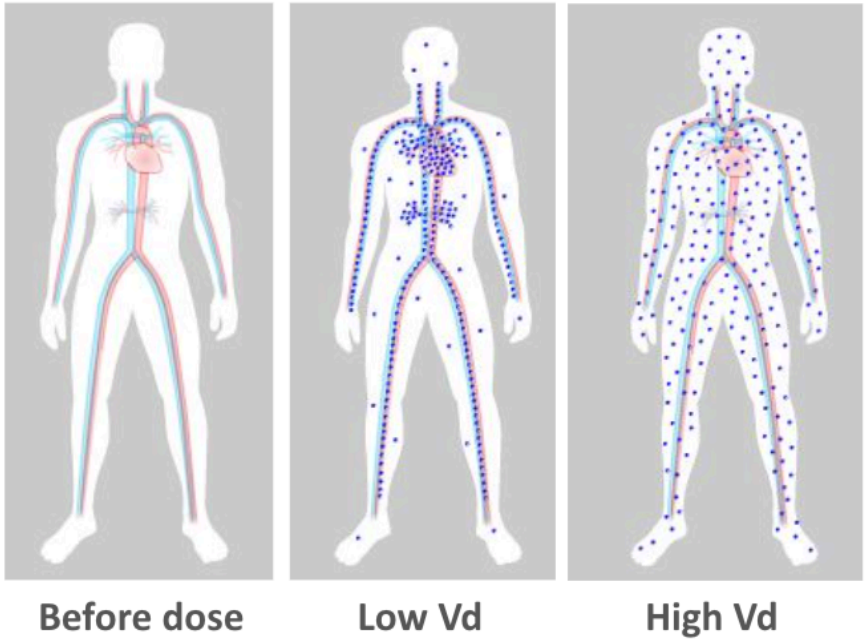
Key pharmacokinetic variable: Volume of distribution (Vd)

- 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

Key pharmacokinetic variable: Volume of distribution (Vd)



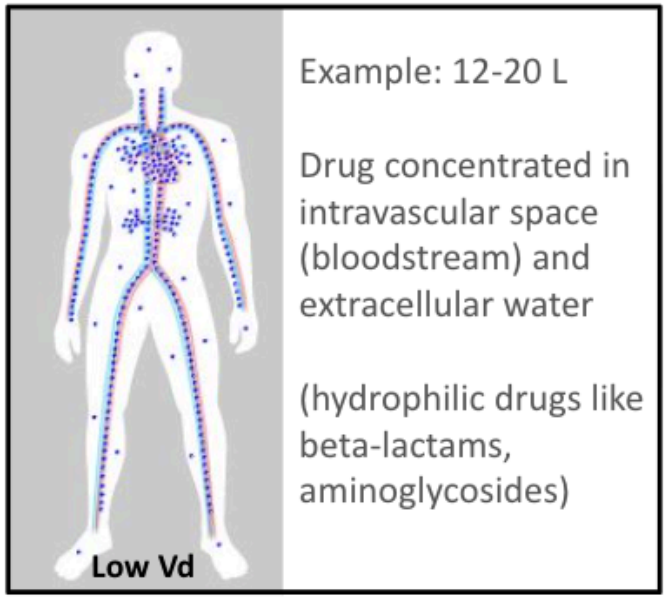
Volume of distribution



- Plasma volume= 3L+ Extracellular water 16 L = Total body water (~20L)
- Higher Vd (e.g., > 46 L Vd)= sequestered in depot (e.g., fat) and serum concentrations will be lower

Volume of distribution (Vd): relevance for antibiotic selection

Provides information on how much antibiotic is distributed in tissues vs. plasma → clinically important

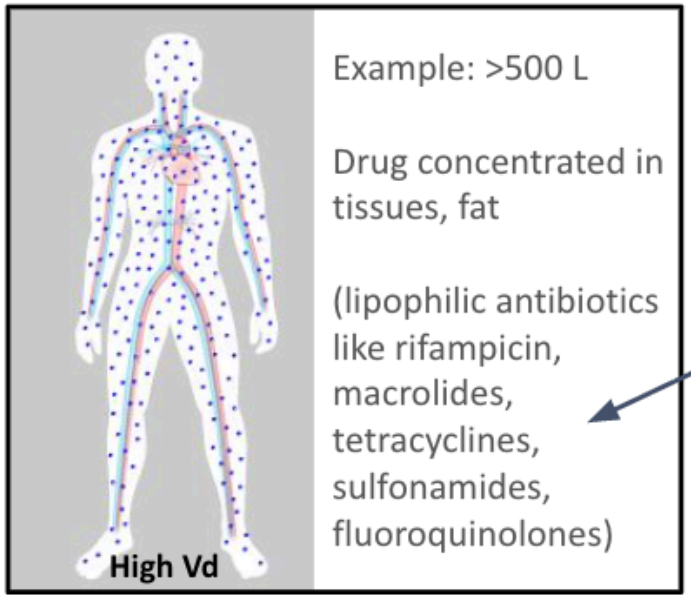


Example: 12-20 L

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

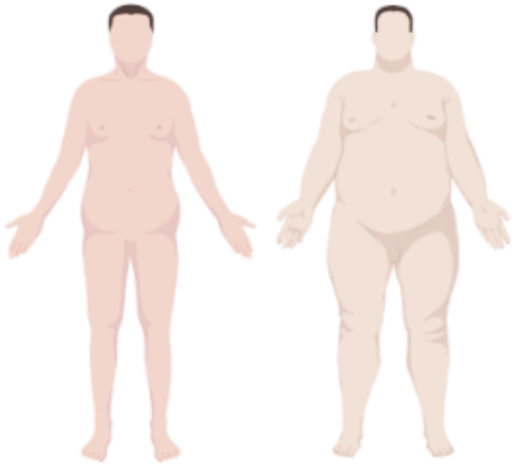
(lipophilic antibiotics like rifampicin, macrolides, tetracyclines, sulfonamides, fluoroquinolones)

Tissue > bloodstream

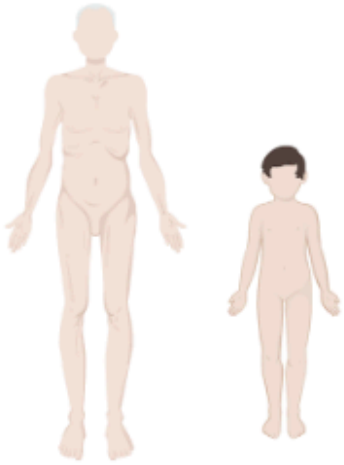
e.g., doxycycline, tigecycline do not achieve peak concentrations in bloodstream that surpass the MIC of many pathogens

Vd alterations

Body mass

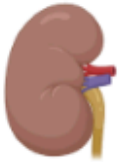


Age, Sex



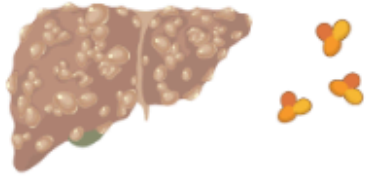
Pregnancy

Kidney disease (e.g., uremia)



uremia decreases drug tissue binding, ↓Vd

Liver disease (e.g., cirrhosis)

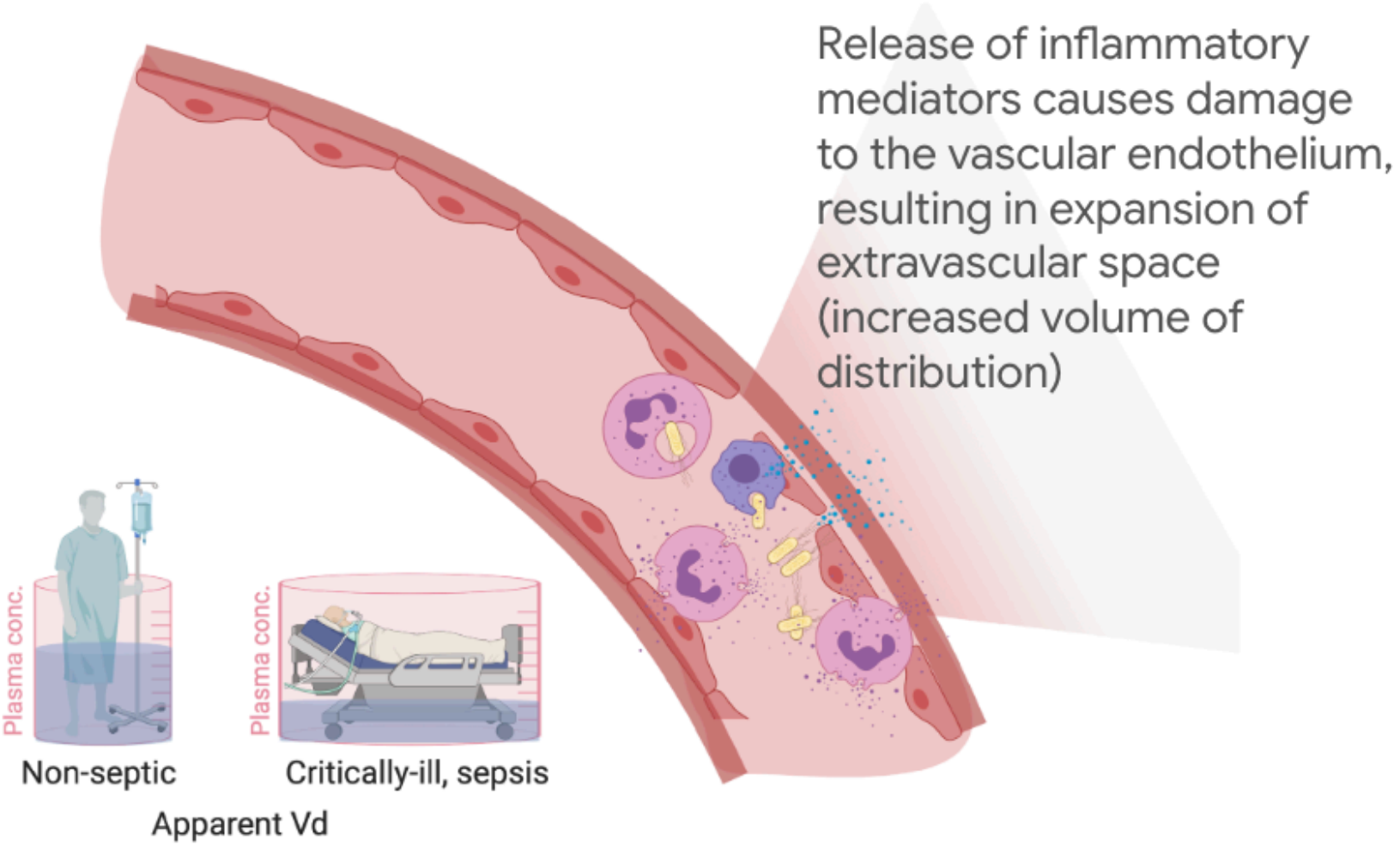


decreased protein production and binding to drugs, ↑ Vd

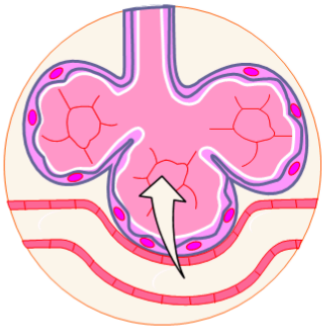
Drug interactions

displaced protein binding of drug, ↑Vd

Vd changes in critical illness



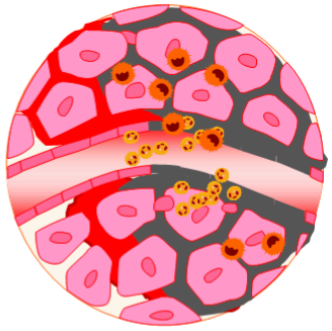
Drug penetration in ventilator-associated pneumonia



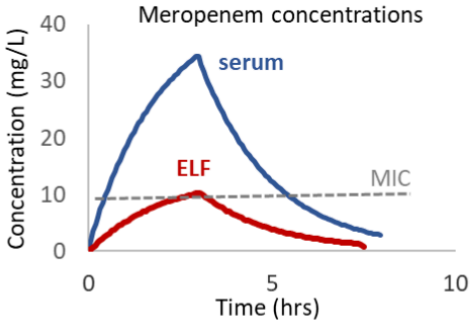
Antibiotic penetration through alveolar capillary barrier (*zona occludens*) by free, non-protein bound drug.

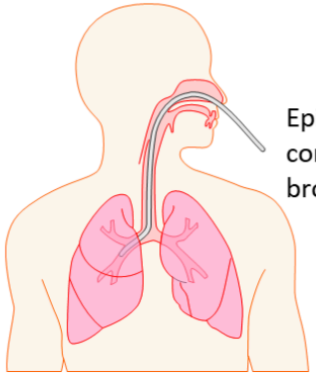
Must cross a transit area cleared by lymphatics

Enhanced by drug lipophilicity



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

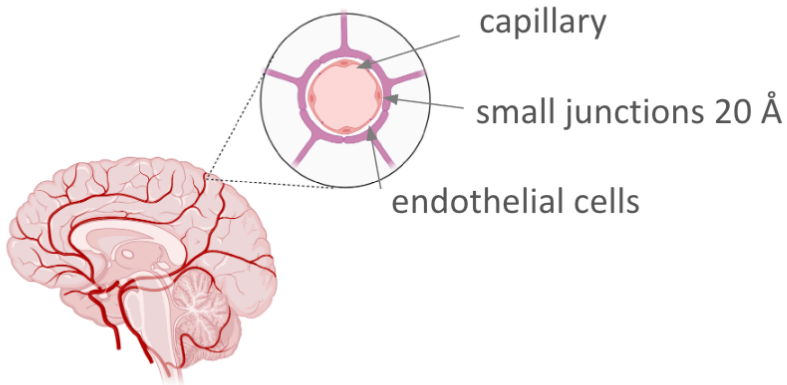




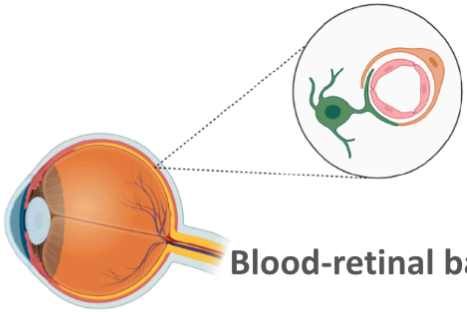
Epithelial lining fluid (ELF) concentrations sampled by bronchoscopy

Anatomically-privileged sites

Anatomically-privileged sites

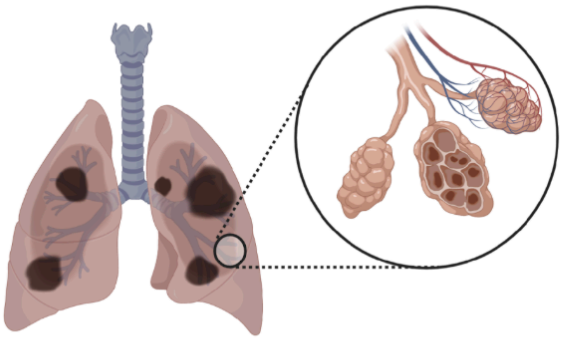


Blood-brain barrier



Blood-retinal barrier

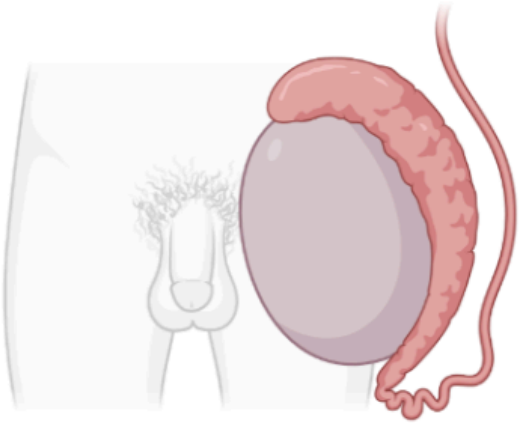
Inflammation, abscess, necrosis



Antibiotic penetration influenced by:

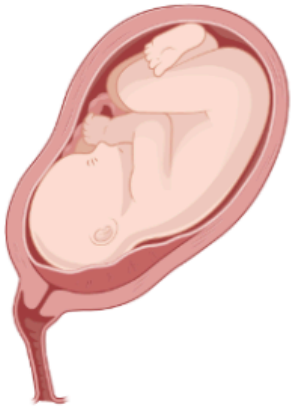
- Serum drug concentrations
- Physicochemical properties of drugs
- Alterations in anatomic permeability (e.g., inflammation)
- Physiological barriers (e.g., blood-eye, blood brain barrier)
- Drug inactivation due to local pH, anaerobic conditions or enzyme activity

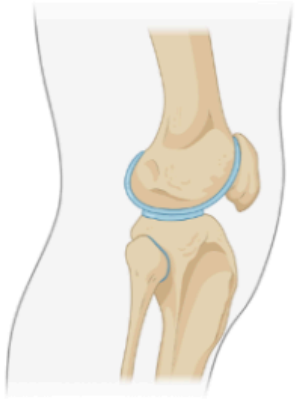
Anatomically-privileged sites



Testicles

Placenta

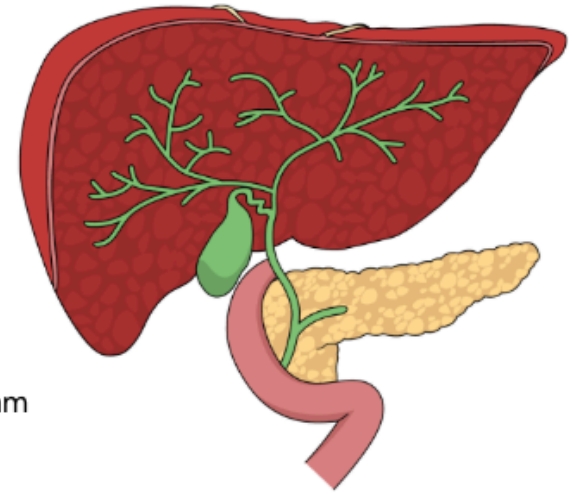




Joint spaces

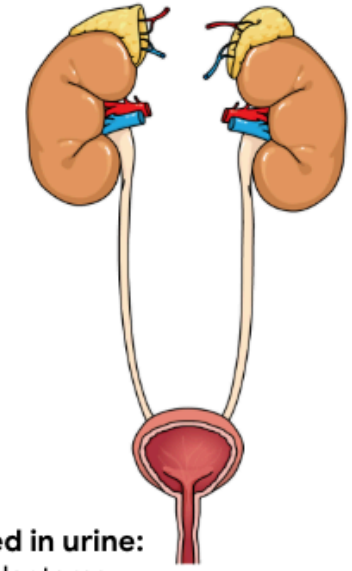
Match the antibiotic to site of infection

Biliary tree (cholecystitis)



Excreted in bile:
Ampicillin
Ceftriaxone
Piperacillin-Tazobactam
Doxycycline

Urinary tract



Excreted in urine:
Most β-lactams
Gentamicin
Ciprofloxacin (but not moxifloxacin)

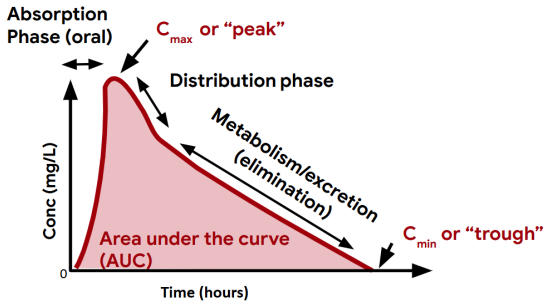
Urinary concentrations of antibiotics

Table 1. Serum and urine concentrations of selected antimicrobials[a]

Drug	Dose, Route	Excretion *via*	Peak Serum Concentration (μg/ml)	% Renal Excretion of Unchanged Drug	Urine Concentration (μg/ml)
β-Lactams					
ampicillin	0.5 g p.o.	GF, TS	3 to 6	75 to 92	1000 to 2250
amoxicillin	0.5 g p.o.	GF, TS	6 to 10	60 to 98	300 to 1300
aztreonam	1 g IV	GF, TS	125	65 to 94	1000 to 5000
piperacillin	3 g IV	GF, TS	209	74 to 89	8000
ticarcillin	3 g IV	GF, TS	257	80 to 99	650 to 2500
cephalexin	1 g p.o.	GF, TS	32	91 to 100	5000 to 10,000
cefuroxime	1 g p.o.	GF, TS	14	50	1000 to 7000
cefixime	0.2 g p.o.		1 to 4	20 to 50	
cefdinir	0.3 g p.o.		1.6	18	21 to 139
cefpodoxime	0.2 g p.o.		2.3	29 to 33	20
cefazolin	1 g IV	GF, TS	188	90 to 96	700 to 2000
ceftriaxone	1 g IV	GF	130	65 to 95	549 to 995
imipenem	0.5 g IV	GF, TS	21 to 58	5 to 42	500
meropenem	1 g IV	GF, TS	50	62 to 83	N/D
ertapenem	1 g IV		154	38	N/D
Fluoroquinolones					
ciprofloxacin	0.5 g p.o.	GF, TS	1.6 to 2.9	30 to 50	350
gatifloxacin	0.4 g p.o.		4.2	65	N/D
gemifloxacin	0.320 g p.o.		0.7 to 2.6	<35	N/D
levofloxacin	0.5 g p.o.	GF	5.7	61 to 86	286
moxifloxacin	0.4 g p.o.		4.5	20	N/D
Miscellaneous					
nitrofurantoin	0.1 gm p.o.	GF, TS, TR	<2	27 to 56	50 to 200
trimethoprim sulfamethoxazole	0.16/0.8 g p.o.		9/105	50 to 75/10 to 30	31 to 165/10 to 133
trimethoprim	0.2 gm p.o.	GF, TS	2	50 to 75	70 to 100
sulfamethoxazole	0.8 g p.o.	GF, TS, TR	46	N/D	400 to 2000
Aminoglycosides					
amikacin	0.5 g IV	GF, TR	17 to 25	>90	170 to 1720
gentamicin	0.08 g IV	GF, TR	4 to 8	>90	400 to 500
tobramycin	0.08 g IV	GF, TR	4 to 8	>90	94 to 443

[a]The urine concentration is expressed as the range of concentrations achieved after a standard dose in patients with normal renal function. Single values represent the average urine concentration over a standard dosage interval (21–23). GF, glomerular filtration; IV, intravenously; N/D, no data; p.o., orally; TR, tubular reabsorption; TS, tubular secretion.

Second key pharmacokinetic variable: Clearance (CL)



- **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.
- **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

Most antibiotics are eliminated via the kidneys and maintenance doses must be adjusted for renal function

14:32 Wed 13 Sep 45%

Meropenem

Contents

(meningitis, CF)	120 mg/kg/day (divided q8h)	6 gm

RENAL ADJUSTMENT

- Body weight and Creatinine Clearance calculations

Half-life (Normal/ESRD)/hr	1/10
Reference Dose Normal Renal Function	1 gm q8h
CrCl > 50-90	1 gm q8h
CrCl 25-50	1 gm q12h
CrCl 10-25	0.5 gm q12h
CrCl < 10	0.5 gm q24h
Hemodialysis	0.5 gm q24h (give dialysis day dose AD)
CAPD	0.5 gm q24h
CRRT	1 gm q12h
SLED	0.5 gm q8h (Crit Care 22:25, 2018)

- CrCl = Creatinine clearance level (mL/min)
- CAPD = Continuous Ambulatory Peritoneal Dialysis
- CRRT = Continuous Renal Replacement Therapy
- AD = after hemodialysis

HEPATIC ADJUSTMENT

- None

OTHER ADJUSTMENT

- Obesity: None
- ECMO: No dosing adjustment required. See ECMO Drug Dosing Adjustment page for more information.

ADVERSE EFFECTS

- Treatment stopped due to adverse effects (1.2%), local phlebitis (1%), hypersensitivity (3%), rash, anaphylaxis, positive Coombs, neutropenia, eosinophilia, thrombocytopenia, nausea/vomiting (4%), diarrhea (5%), increased LFTs (4%), headache (3%).

Guide Bookmarks Calculator Add-Ons Account

Estimating renal function

Cockcroft-Gault formula (other formulas MDRD...etc.)

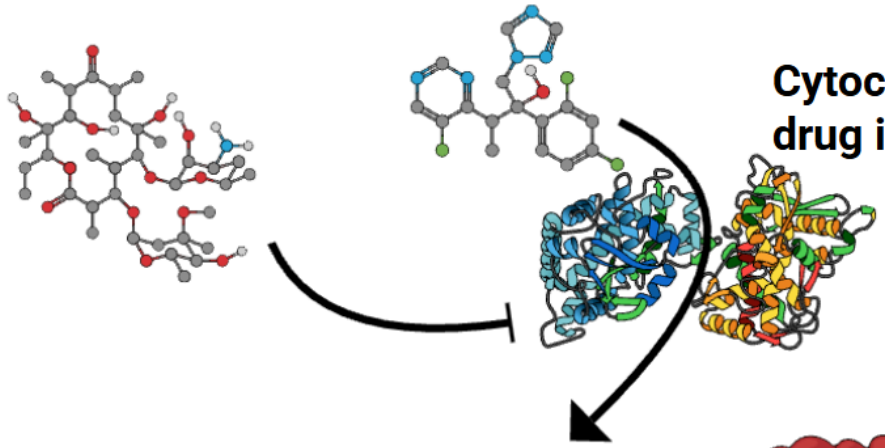
$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{SCr (mg/dL)}} \times 0.85 \text{ (if female)}$$

- Formula developed primarily in Caucasian males with chronic renal disease
- Does not take into account effects on older age, comorbidities and drug interactions with renal tubular secretion
- Antibiotic dosing in dialysis (drug-specific dosing guidance)

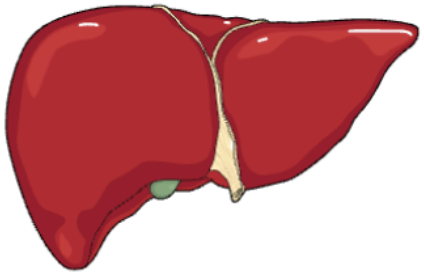
Problems of using serum creatinine-based dosing adjustments

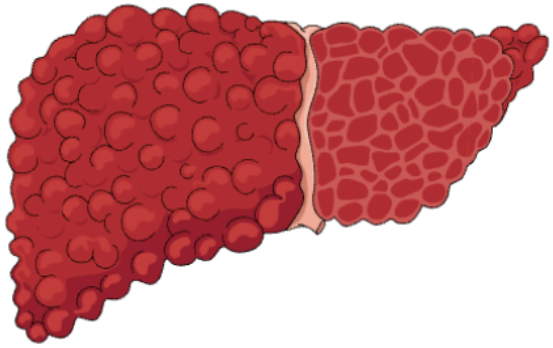
- Antibiotic renal dose adjustments in drug labels are based on patients with chronic kidney disease
- Renal impairment is acute, not chronic, in up to 50% of patients with infection **and frequently resolves within the first 48 hours**
- Creatinine-based equations for estimates of CrCl are based on 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**

Hepatic clearance of antibiotics



Cytochrome P450 and other enzyme drug interactions





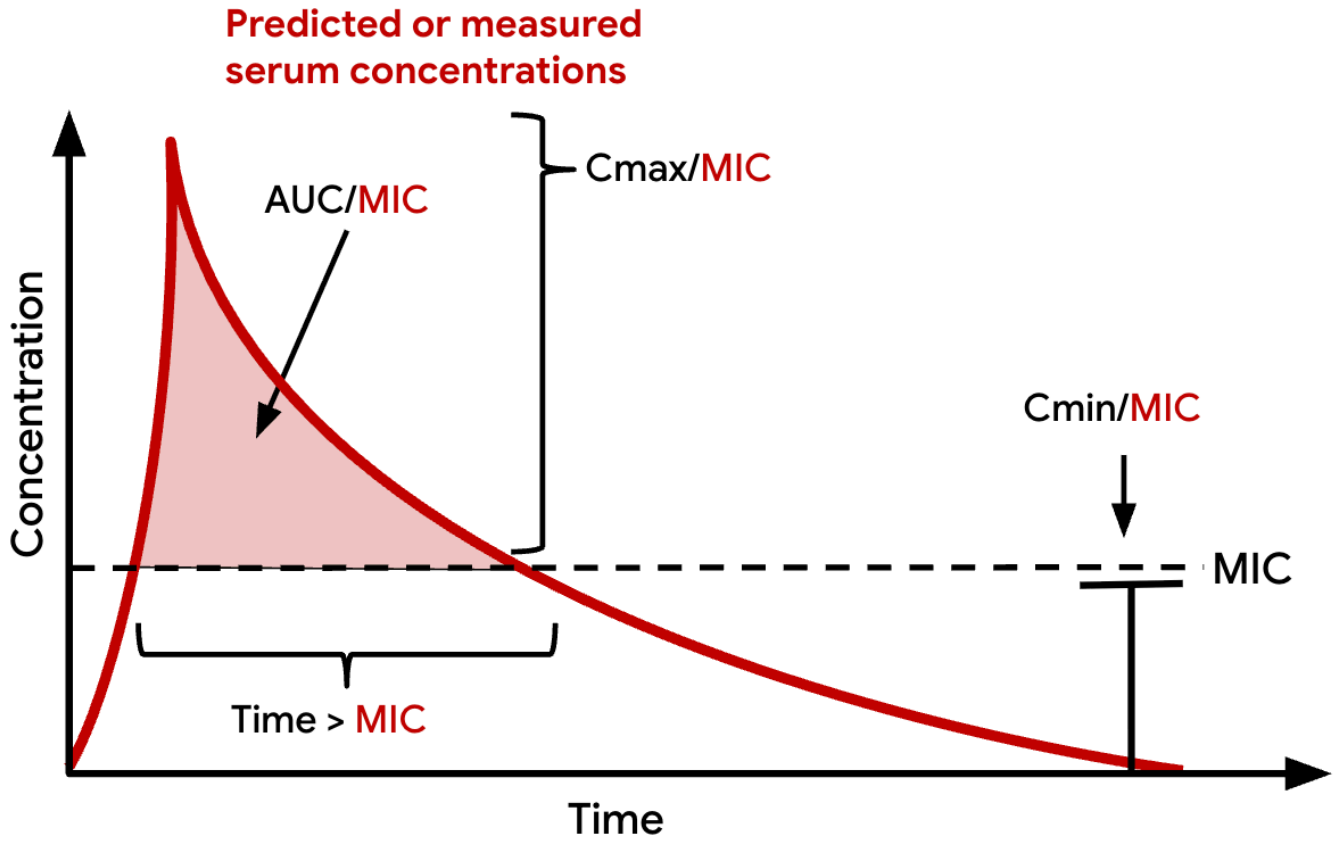
Acute liver dysfunction

Chronic liver cirrhosis (Child Pugh Score)

Drug interaction screening

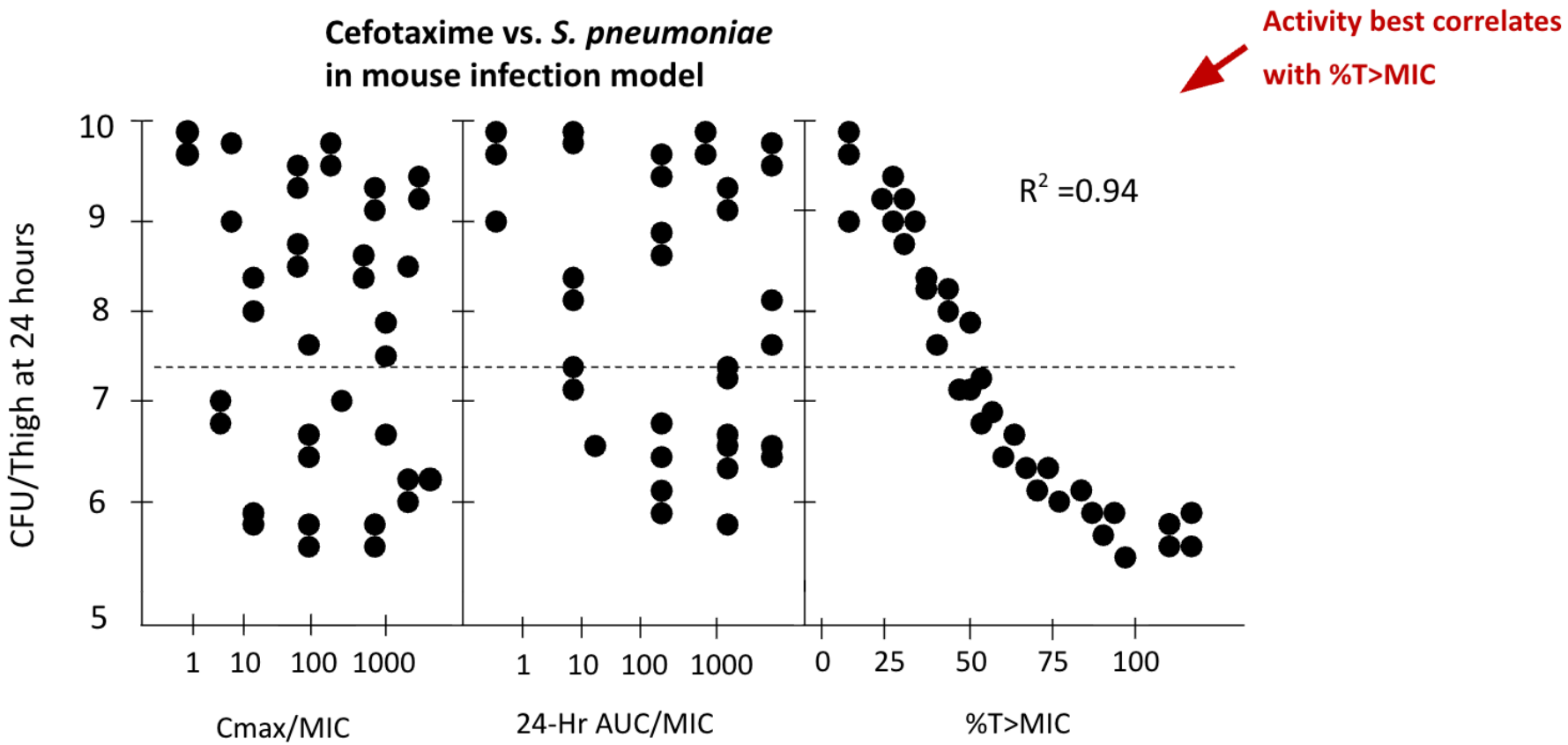
https://www.uptodate.com/contents/search
UptoDate

PK/PD indices

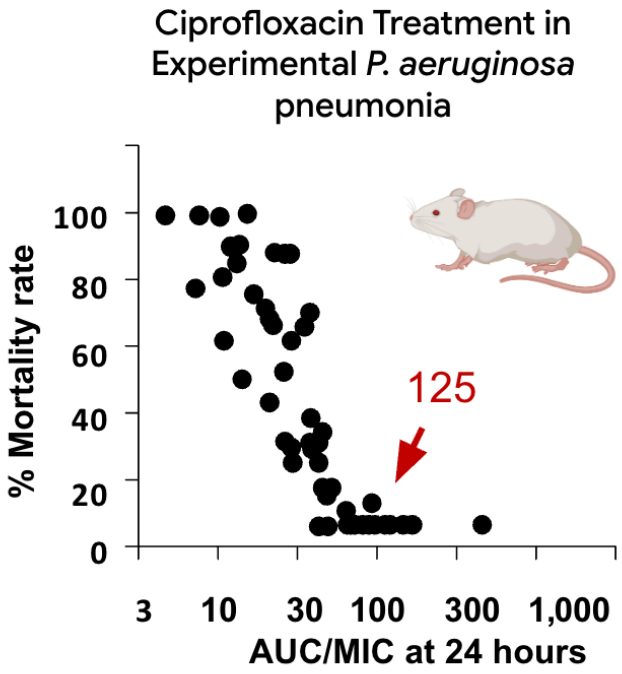


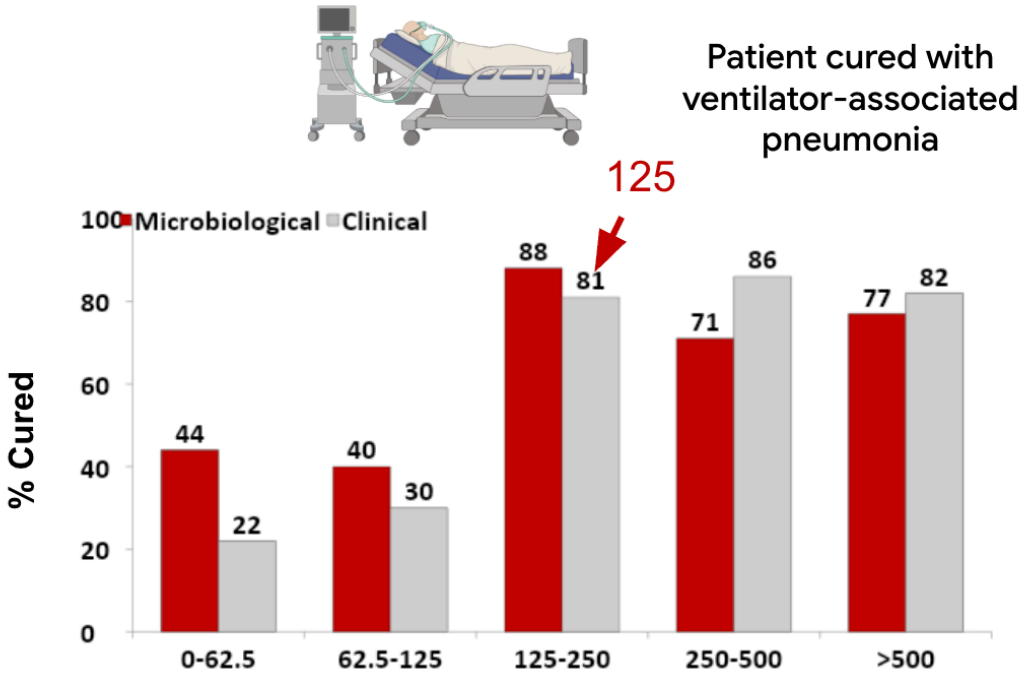
AUC = Area under the concentration–time curve; MIC = Minimum Inhibitory Concentration; C_{max} = Maximum or peak plasma concentration; C_{min} = Minimum or trough plasma concentration

How are PK/PD indicies identified?



Do PK/PD indices correlate with clinical outcome of antibiotic therapy





PK/PD characteristics of common antibiotic classes

	Cmax/MIC	AUC/MIC	T>MIC
Examples	Aminoglycosides Fluoroquinolones Polymyxins	Azithromycin Fluoroquinolones Ketolides Linezolid Daptomycin Vancomycin Tigecycline	Penicillin Cephalosporins Carbapenems Monobactams Macrolides
Organism kill	Concentration dependent	Concentration and time dependent	Time-dependent
Dosing goal	Maximize exposure (multiples of MIC)	Maximize exposure over time (multiples of MIC over time)	Optimize duration of exposure (time above MIC)

Cmax/MIC ratio of peak antibiotic concentrations to MIC; AUC/MIC relationship of area of the the curve to MIC; T> MIC, time antibiotic concentrations surpass the MIC

TDMx for Meropenem

UI version: 0.98.0 beta

TDMxR version: 0.3.2

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Prof. Dr. Sebastian G. Wicha

c/o Institute of Pharmacy, University of Hamburg, Germany

Welcome to TDMx

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Do you want to reload a previously saved patient or continue with a new patient?

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Information to users:

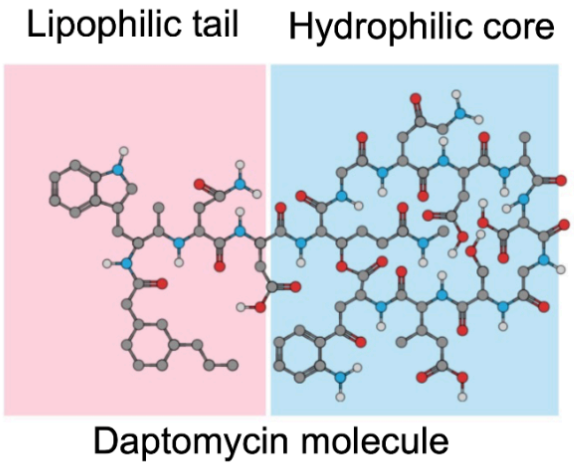
This is a beta version! You can improve TDMx by reporting any bug/issue you observe! Just email us! (mailto:info@tdmx.eu)

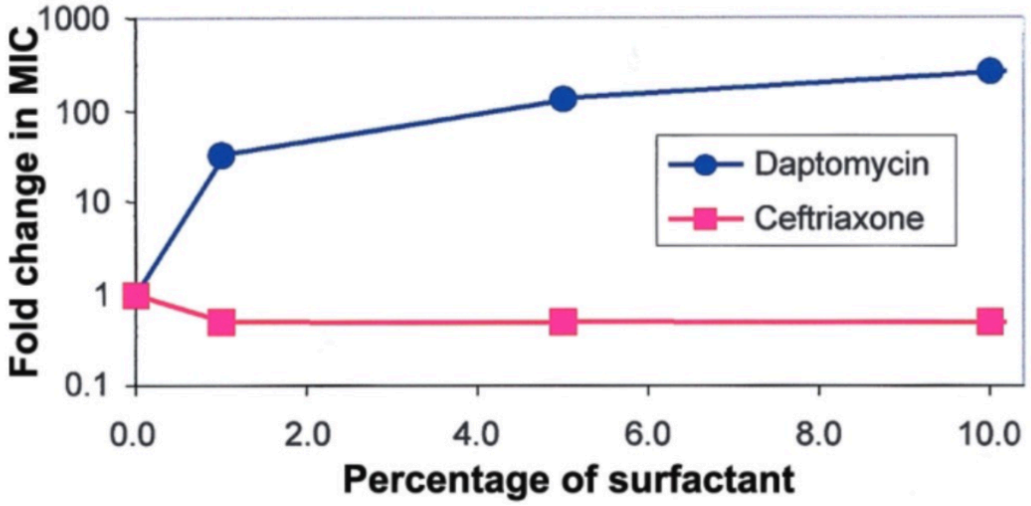
References

Population PK model: Li et al. J Clin Pharmacol, 2006: 1171-8 (http://www.ncbi.nlm.nih.gov/pubmed/16988206)

Population PK model: Ehmann et al. Int J Antimicrob Agents, 2019: 309-17 (https://pubmed.ncbi.nlm.nih.gov/31229669/)

Daptomycin is inactivated in the lung

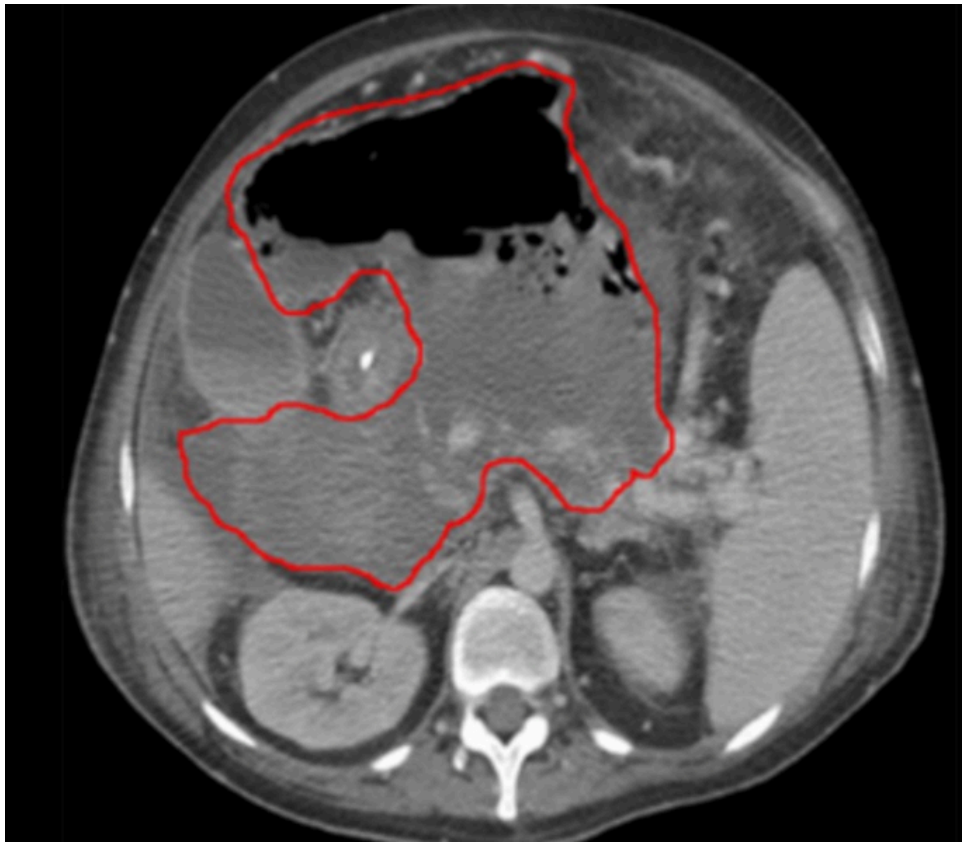




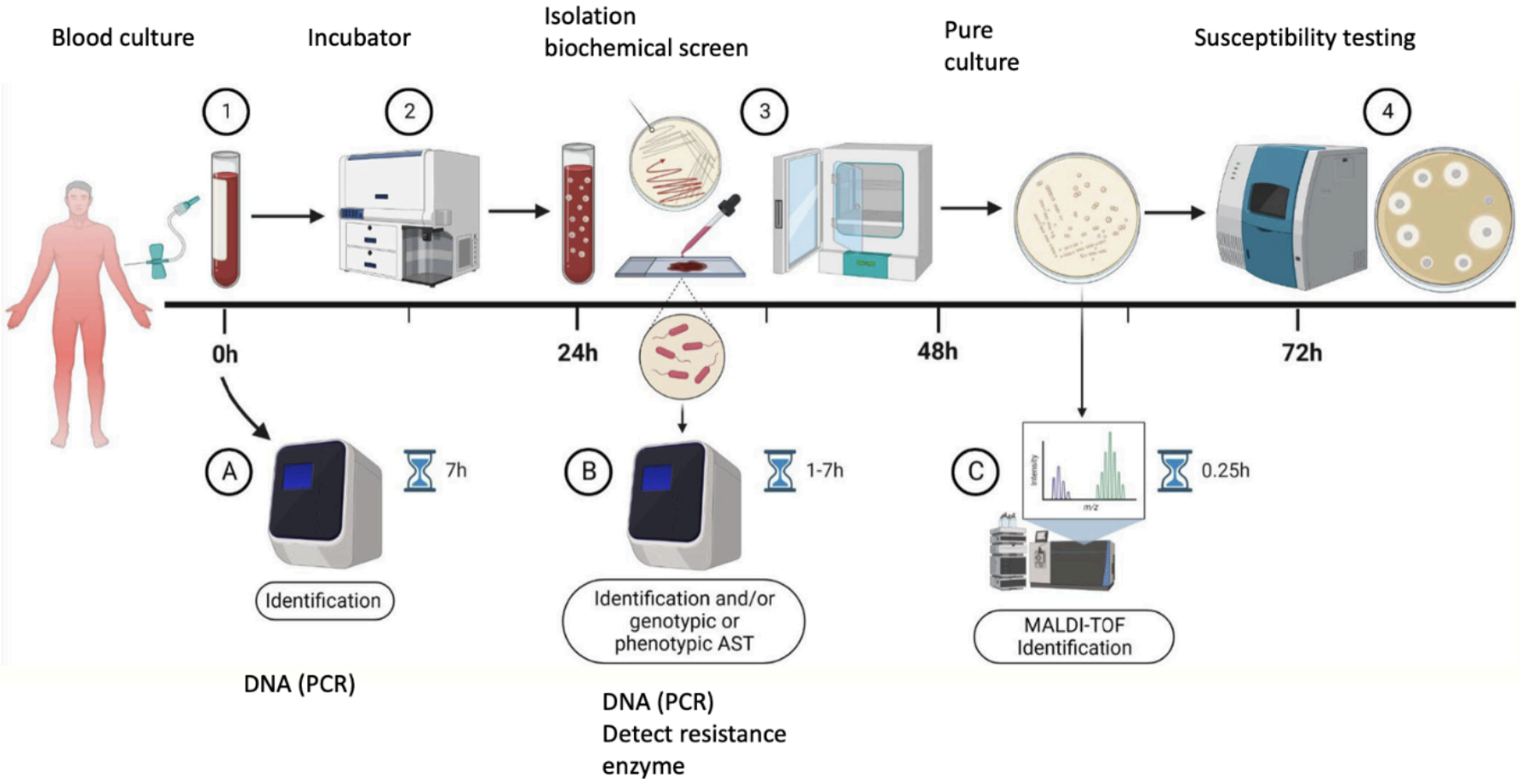
Antibiotic activity in abscess

Aminoglycosides

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



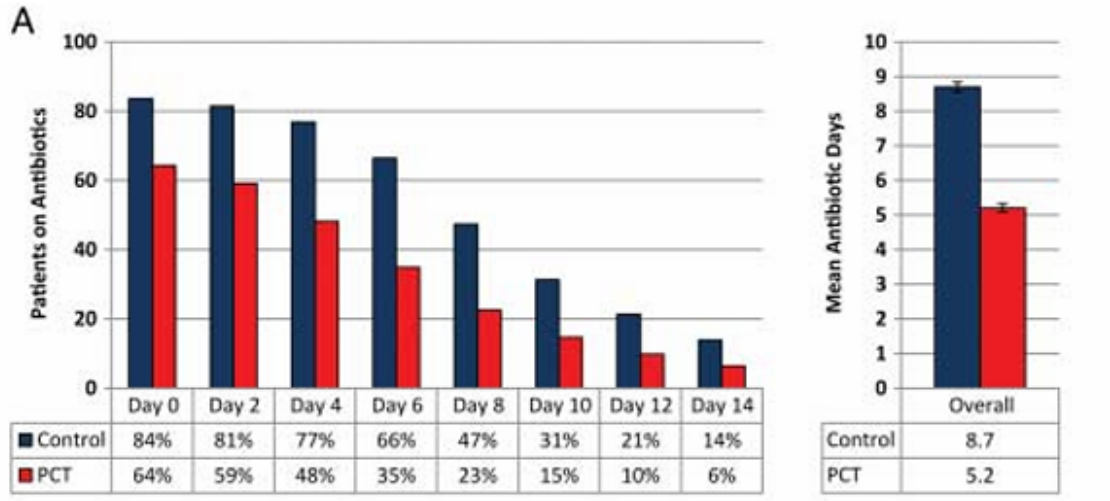
Principle #7: De-escalate antibiotic therapy based on microbiology results and clinical (biomarker) responses



Antibiotic de-escalation

- **De-escalation with pathogen identification**
  - e.g., stopping empirical vancomycin in patient with Gram-negative bacilli in blood cultures
- **Clinical improvement-reduction in fever and leukocytosis**
- Empiric de-escalation of therapies for highly-resistant pathogens if they have not grown from culture
  - e.g., stopping empirical vancomycin in a patient without positive MRSA cultures
- **Biomarkers:** C-reactive protein (clinical utility questioned), procalcitonin - *areas of diagnostic stewardship as tests are frequently abused*

Incorporation of procalcitonin into therapeutic decisions reduces antibiotic use



	Day 0	Day 2	Day 4	Day 6	Day 8	Day 10	Day 12	Day 14
Control	84%	81%	77%	66%	47%	31%	21%	14%
PCT	64%	59%	48%	35%	23%	15%	10%	6%

	Overall
Control	8.7
PCT	5.2

Choosing therapy : gram-stain vs. guidelines

RCT: Effect of Gram Stain–Guided Initial Antibiotic Therapy on Clinical Response in Patients with Ventilator-Associated Pneumonia

POPULATION

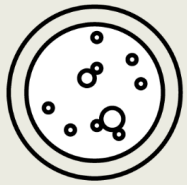
141 Men, 65 Women

Adolescents and adults ≥15 y with ventilator-associated pneumonia

Median (IQR), 69 (54-78) y

INTERVENTION

206 Participants randomized



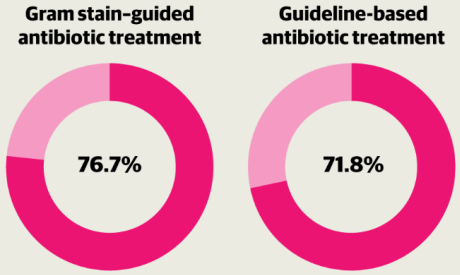
103 Gram stain–guided antibiotic treatment
Empiric antibiotics chosen based on endotracheal aspirate Gram stain results

103 Guideline-based antibiotic treatment Antibiotics chosen based on Infectious Disease Society of America and American Thoracic Society guidelines

FINDINGS

Clinical response in the Gram stain–guided antibiotic treatment group was noninferior to the guideline-based antibiotic treatment group

Proportion of participants with clinical response



Risk difference:
0.05 (95% CI, −0.07 to 0.17); *P*<.001 for noninferiority

SETTINGS / LOCATIONS

12 Intensive care units in Japan

PRIMARY OUTCOME

Noninferiority of clinical response at 7 d after therapy, defined as antibiotic completion within 14 d + no radiographic progression from baseline + resolution of pneumonia signs/symptoms + no antibiotic readministration

Yoshimura J, Yamakawa K, Ohta Y, et al. Effect of gram stain-guided initial antibiotic therapy on clinical response in patients with ventilator-associated pneumonia: the GRACE-VAP randomized clinical trial. *JAMA Netw Open*. 2022;5(4):e226136. doi:10.1001/jamanetworkopen.2022.6136

- Gram strain guided therapy resulted in a 30% reduction in use of anti-pseudomonal agents and 40% reduction in MRSA agents
- Gram-stain guided therapy resulted in higher rate of appropriate antibiotic escalation (7% vs. 1%, p=0.03)

Emocoltura

Esame colturale — Pervenuto flacone: Anaerobio, Aerobio

1° Isolamento : Klebsiella pneumoniae
Positivizzato il 02/08/2023 21:18:43
da periferico
Ceppo produttore di carbapenemasi KPC. Si raccomanda di utilizzare le precauzioni standard e da contatto per prevenirne la diffusione. La terapia con carbapenemi potrebbe risultare scarsamente efficace o inefficace, si consiglia di contattare un esperto di terapia antibiotica.
MIC Tigeciclina 2
MIC Imipenem-relebactam 0.19 S
Merepenem-Vaborbactam 0.32 S
KB Cefiderocol 22mm S

Antibiogramma

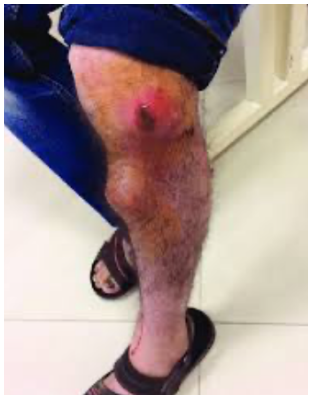
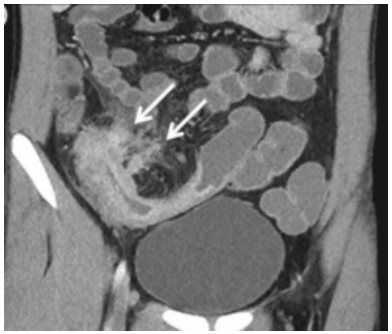
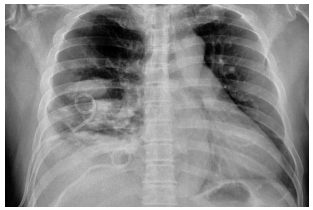
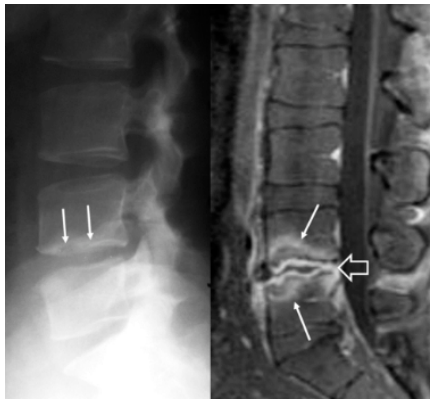
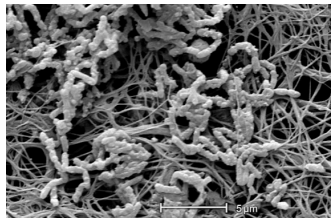
Klebsiella pneumoniae

	SIR	MIC	Valori MIC (microdiluizioni in brodo)
CEFTAZIDIME/AVIBACTAM	S	<= 1	1 2 4 8 | 16 32 64
COLISTINA	S	1	0.5 1 2 | 4
AMIKACINA	S	<= 4	4 8 | 16
PIPERAC.-TAZOBACTAM	R		
CEFTRIAXONE	R		
GENTAMICINA	R		
MEROPENEM	R		
TRIMETH/SULFA 1/19	R		
CEFEPIME	R		
CEFTAZIDIME	R		
AMOXACILLINA/CLAVULAN	R		
CIPROFLOXACINA	R		

Principle #8: If therapy is not working, consider source control or alternative diagnosis before assuming resistance and broadening therapy

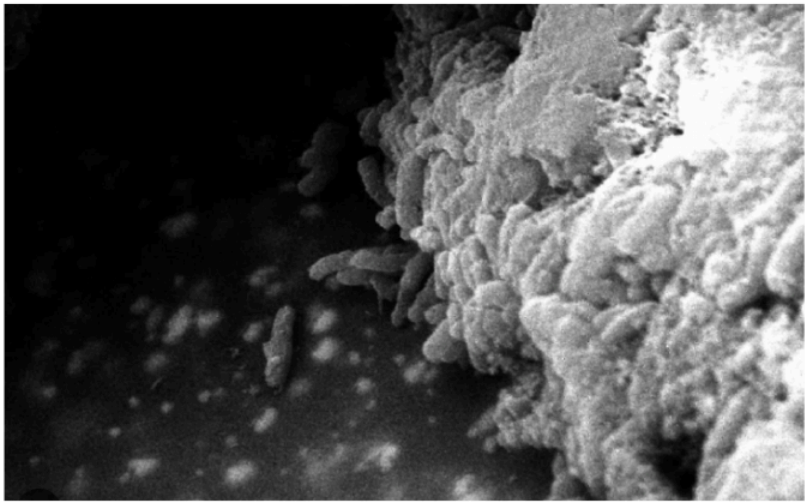
- Consider changing antibiotics of the following parameters do not improve:
  - Fever curve
  - White blood cell count
  - Purulent secretions
  - Signs of inflammation (*rubor, tumor, dolor, calor)*
  - Biomarkers (procalcitonin)

Source control

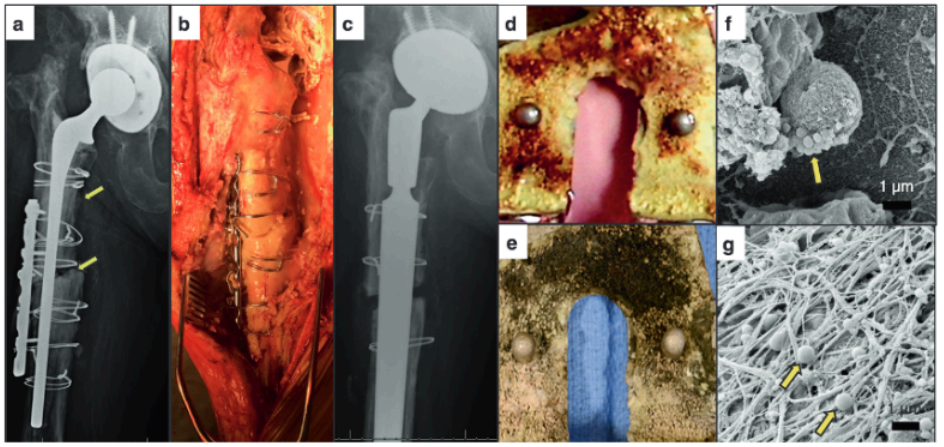
Occult subcutaneous abscess in cellulitis	New abscess formation in intraabdominal infection	Empyema in community-acquired pneumonia	Visceral or skeletal abscess in patient with bacteremia	Failure to remove a central venous catheter
				

Biofilms: A key source of antibiotic failure

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

Antibiotic FAIL

- **F**alse diagnosis
- **A**llergies
- **I**ntercurrent infections
- **L**ocalized process

Principle #9: Distinguish new infection from failure of initial therapy

- **New onset of infectious signs, symptoms, and biomarkers after resolution of prior infection should raise the concern of a new infection rather than persistence of the original infection**
- **Rarely, recrudescence of signs and symptoms may reflect emergence of antibiotic resistance on therapy from the initial pathogens**
  - This may be seen more with specific bacterial pathogens, such as *Acinetobacter baumannii*, than with others
  - An initial apparent response to infection followed days or weeks later by new onset of infectious signs or symptoms should prompt a complete reevaluation of the patient for a new infection, including reculturing and imaging if necessary
- **I*n these patients, it is generally reasonable to broaden therapy to cover highly resistant pathogens**
  - Such patients have been exposed to recent courses of antibiotics and have a higher risk of being infected by antibiotic-resistant pathogens
- **When changing antibacterial therapies because of breakthrough infection or lack of response to initial therapy, it is generally advisable to change one antibiotic at a time (to a different class if possible)**

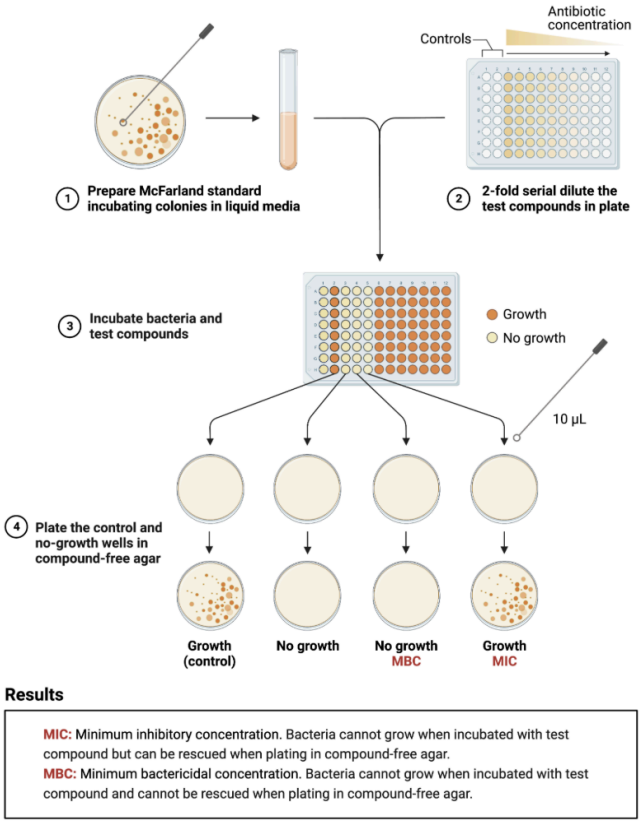
Principle #10: The duration of therapy should be as short as possible based on evidence

Disease	Short course (days)	Long course (days)	Outcome
Bacteremia, gram-negative	7	14	Equivalent
Chronic bronchitis and COPD	≤ 5 days	≥ 7	Equivalent
Intra-abdominal infection	4	10	Equivalent
Neutropenic fever	Until afebrile and stable	Until, afebrile, stable and non-neutropenic	Equivalent
Osteomyelitis, chronic	42	84	Equivalent
Pneumonia, community-acquired	3-5	7-10	Equivalent
Pneumonia, nosocomial (including VAP)	≤ 8	10-15	Equivalent
Pyelonephritis	5-7	10-14	Equivalent
Skin infections (cellulitis, major abscess, wound infections)	5-6	10-14	Equivalent
Sinusitis, acute bacterial	5	10	Equivalent

Common myths of antibiotic therapy

Myth 1:
“Bactericidal” antibiotics are more effective than “bacteriostatic”

- Bactericidal activity: concentration of drug that results in 1000-fold reduction in inoculum within 24 hours
- Bactericidal antibiotic: MBC of drug is 4-fold or less above the MIC



Systematic literature reviews: *cidal vs. static* antibiotics for bacterial infections*

- 56 randomized controlled trials identified
- 49/56 found no difference in clinical outcomes, including highly-lethal infections in critically-ill patients
  - Typhoid fever, severe pneumonia, severe sepsis
- 6 trials reported linezolid (static antibiotic) to be superior to “cidal” agents (vancomycin, teicoplanin or cephalosporins)
- 1 trial found imipenem superior to tigecycline in ventilator associated pneumonia- however tigecycline dosage was too low:
  - A subsequent study using double to dose of tigecycline found no difference

Other examples where more rapid bactericidal activity failed to show clinical superiority

- Daptomycin (rapidly bactericidal) vs. vancomycin (slowly bactericidal) against *Staphylococcus aureus* bacteremia and right-sided endocarditis
- Addition of aminoglycosides to ß-lactams or ß-lactams to vancomycin/daptomycin results in more rapid kill of staphylococci, but in clinical trials no improvement in outcomes and higher rates of nephrotoxicity
- Bacterial endocarditis: Historical artifact?
  - Early studies compared high Vd drugs (tetracyclines, marcolides) to penicillins (low Vd drugs) for endocarditis
  - Low blood concentrations with tetracyclines and macrolides makes them a poor choice for high-grade bloodstream infections

Myth 2: Oral antibioic therapy is less effective than IV for complex infections

- **Osteomyelitis**: Earlier studies with oral sulfanilamide, erythromycin, tetracycline with low blood and bone concentrations were associated with higher failure rates-did not surpass pathon MICs
- **However**, numerous modern antibiotics can acheive levels in blood and bone that are well in excess of target pathogen MICs

Oral is the new IV

Osteomyelitis | Bacteremia | Endocarditis

Study or Subgroup	Oral Events	Oral Total	IV Events	IV Total	Weight	Risk Difference M-H, Random, 95% CI	Year
Greenberg 1987	7	14	11	16	1.2%	-0.19 [-0.53, 0.16]	1987
Mader 1990	11	14	10	12	1.7%	-0.05 [-0.35, 0.25]	1990
Gentry 1990	24	31	22	28	3.3%	-0.01 [-0.22, 0.20]	1990
Gentry 1991	14	19	12	14	2.1%	-0.12 [-0.39, 0.15]	1991
Gomis 1999	11	16	8	16	1.3%	0.19 [-0.15, 0.52]	1999
Schrenzel 2004	18	22	11	17	1.9%	0.17 [-0.11, 0.45]	2004
Euba 2009	17	21	21	27	2.8%	0.03 [-0.20, 0.26]	2009
Li 2019	457	527	450	527	85.6%	0.01 [-0.03, 0.06]	2019
Total (95% CI)		**664**		**657**	**100.0%**	**0.01 [-0.03, 0.05]**	
Total events	559		545				

Heterogeneity: Tau² = 0.00; Chi² = 4.74, df = 7 (P = 0.69); I² = 0%

Test for overall effect: Z = 0.61 (P = 0.54)

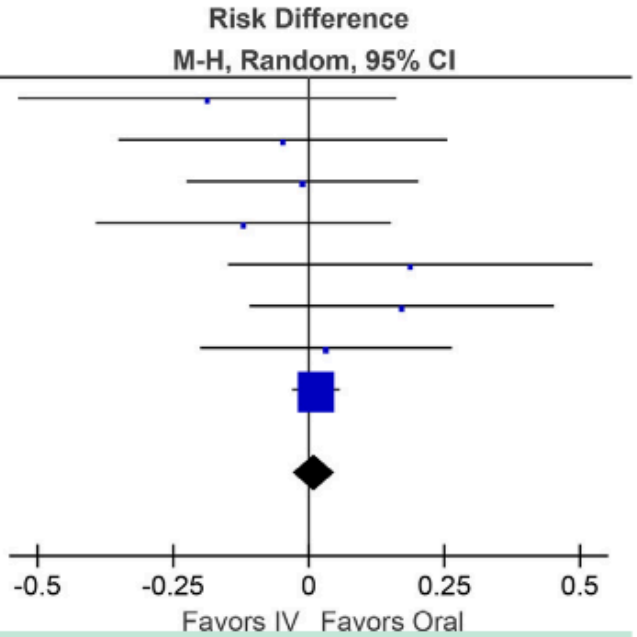


Figure 2 Meta-analysis forest plot of osteomyelitis treatment success. Overall treatment success was not significantly different.

Transitioning to oral therapy: Key considerations

- Is the patient hemodynamically stable?
- Will the patient absorb the medication (functioning GI tract)?
- Can the patient take drugs by mouth
- Do we have an antibiotic option with good bioavailability for the infection?

Oral bioavailability of antibiotics

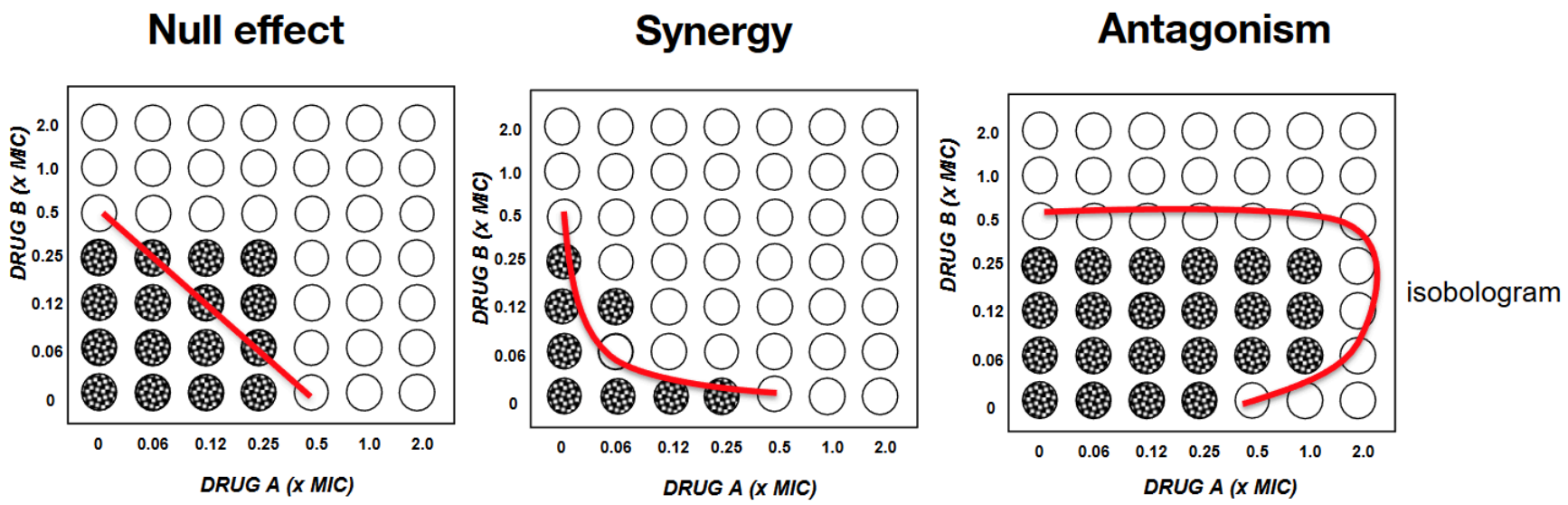
Staphylococcus (MRSA)	**Enterococcus**	**Streptococcus**	**Enterobacterales**	**Pseudomonas**
Linezolid (100%) TMP/SMX (90-100%) Doxycycline (95%) Delafloxacin (90%)	Linezolid (100%) Ampicillin (50%) Nitrofurantoin [urine] (80%) Amox/Clav (85%)	**GAS/GBS** Penicillin VK (50%) Amoxicillin (85%) Cephalexin (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)

Myth #3: Combination therapy: *The good, the bad,…and the ugly*

- Are 2, 3 or 4 drugs better than 1?.....it depends on the situation
- **Synergistic combination** the killing effect of two or more antibiotics is greater than the added effect of each antibiotic by itself
- Clinically, suggests that the success rate (however measured) is better when the two antibiotics are administered simultaneously

Microbiological rationale: Checkerboard test



Null effect (indifference)
$FIC_A + FIC_B = 1.0$

Synergy
$FIC_A + FIC_B \leq 0.5$

Antagonism
$FIC_A + FIC_B > 1.0$ (or ≥4)

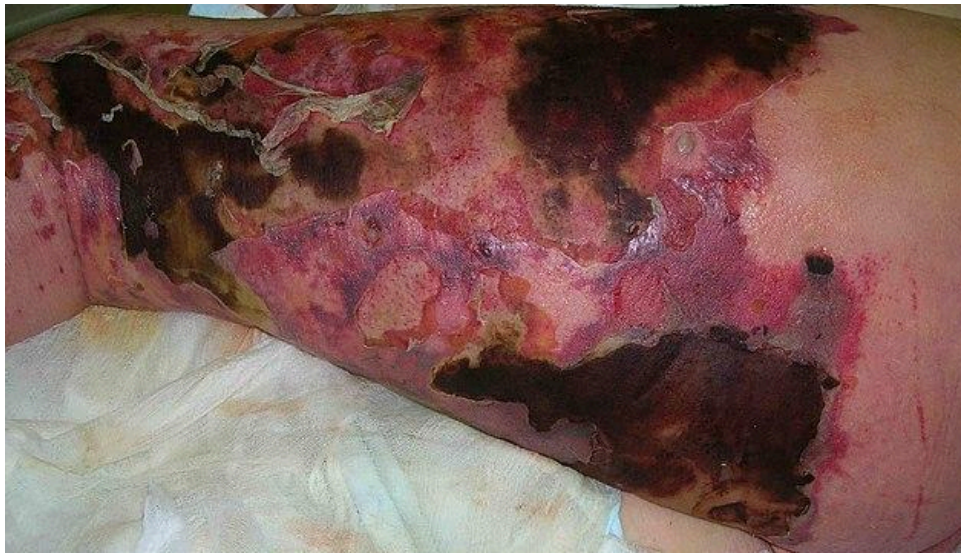
Combination therapy: *The good*

- **Spectrum**: More than one drug is required to provide adequate coverage
  - e.g., adding macrolide or doxycycline to cover atypical pathogens not treated by backbone ß-lactam
  - Specific ICU ward or hospital ward with high rates of MDR- Two drugs may have greater coverage of MDR pathogens
- **Preventing emergence of resistance in specific clinical scenarios**
  - Tuberculosis: Slow growth, non-replicating or low-replicating persister cells and can achieve high bacterial densities in cavitary disease with spontaneous mutations
  - HIV and hepatitis C: Resistance converts a treatable (HIV) or curable (HCV) infection into a fatal illness

Combination therapy: *The good, cont.*

- **Two active agents results in superior clinical outcomes compared to single active agent**
  - Slow growing infection/non replicating persisters- e.g. anti-tubular activity of rifampin and PZA ensure (1) empirical therapy is active; (2) prevent emergence of resistance; (3) improve clinical cure with shorter duration of therapy
  - Bone and joint infections (nonreplicating bacteria in biofilm): Reduced relapse rates with addition of rifampin, especially to fluoroquinolones

Exotoxin-mediated infections- Necrotizing fasciitis



- Streptococci or *Clostriudium* infections that are extremely destructive and aggressive
- Addition of clindamycin or linezolid as a 2nd agent terminates protein synthgesis: shutting down toxin production in the bacteria
- Adding protein synthesis inhibitors to backbone antibacterial therapy has been associated with improved survival in retrospective studies

Eukaryotic infections: Combination therapy is beneficial

- Cryptococcal meningitis (fungal infection): Amphotericin B + 5-FC
- Protozoal infection (*Plasmodium vivax P. ovale*): Primaquine added to backbone therapy to kill hepatic -phase hypnozoites not killed by other agents, which lead to late relapse
- Acute amebic colitis: Metronidazole + luminicidal agent (iodoquinol or paromomycin) to kill encysted, non-meatabolically actuve organisms in the bowel lumen
- Nematode infections: Doxycycline added to ivermectin or albendazole to kill commensal bacteria *Wolbachia*, which play a role in the parasite viability and fertility.
- Neurocystosis: Albendazole plus praziquantel: Dula mechanism of killing and pharmacokinetic interaction leading to higher drug exposures in the CNS and cysts within the sequestered site

Combination therapy *the bad-Redundant definitive therapy for "typical infections"*

- Very few data supporting the use of two active agents for acute, pyogenic bacterial infections
  - Organisms are in planktonic growth, not multiple phases of life cycle
  - No commensal organisms inside the bacteria to kill
  - Pharmacology and killing activity of single agents is good

Combination therapy for *Pseudomonas aeruginosa*

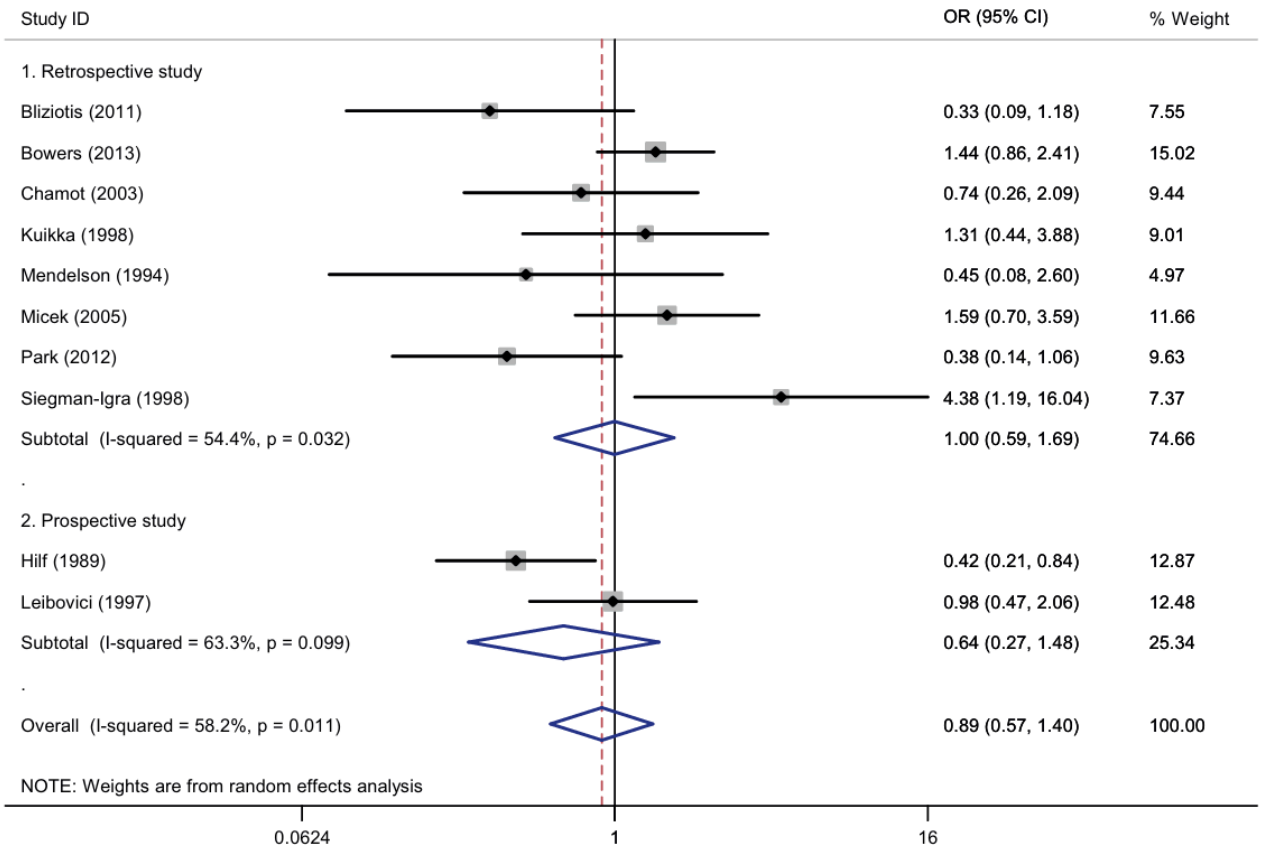


Fig. 2. Forest plot comparing combination therapy with monotherapy for *Pseudomonas aeruginosa* bacteraemia, by study design. OR, odds ratio; CI, confidence interval.

- Combination therapy studies for severe infections/sepsis have also found no advantage for dual therapy
- Dual therapy more likely to result in toxicity and microbiom harm- potential resistance to 2 drug classes

Combination therapy- *The ugly: imperfect data*

- Fungal infections outside cryptococcosis
  - *Candida* infections- no clear benefit
  - *Aspergillus* infection- possible benefit with echinocandins and triazoles

Does combination therapy prevent resistance?

- ***Yes-*** *Tuberculosis, HIV, HCV*
- In test tubes (in theory) may work- *but Pyrrhic victory- greater selection for resistance, greater impact on microbiome?*

Conclusions

- Antibiotic therapy are miracle cures that have fundamentally altered the practice of medicine
- Their incredible power to effectively treat patients is fleeting
- Physicians bear the burden of using antibiotics effectively to heal and cure patients while preserving this awesome power

References

Chastain DB, Spradlin M, Ahmad H, Henao-Martínez AF. Unintended consequences: Risk of opportunistic infections associated with long-term glucocorticoid therapies in adults. Clinical Infectious Diseases 2023:ciad474. https://doi.org/10.1093/cid/ciad474.

Chow AW, Benninger MS, Brook I, Brozek JL, Goldstein EJC, Hicks LA, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America 2012;54:e72–112. https://doi.org/10.1093/cid/cir1043.

Craig WA. Pharmacokinetic/pharmacodynamic parameters: Rationale for antibacterial dosing of mice and men. Clinical Infectious Diseases 1998;26:1–10. https://doi.org/10.1086/516284.

Crass RL, Rodvold KA, Mueller BA, Pai MP. Renal dosing of antibiotics: Are we jumping the gun? Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America 2019;68:1596–602. https://doi.org/10.1093/cid/ciy790.

Gilbert DN. Urinary tract infections in patients with chronic renal insufficiency. Clinical Journal of the American Society of Nephrology 2006;1:327. https://doi.org/10.2215/CJN.01931105.

Hu Y, Li L, Li W, Xu H, He P, Yan X, et al. Combination antibiotic therapy versus monotherapy for pseudomonas aeruginosa bacteraemia: A meta-analysis of retrospective and prospective studies. International Journal of Antimicrobial Agents 2013;42:492–6. https://doi.org/10.1016/j.ijantimicag.2013.09.002.

Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*. Critical Care Medicine 2006;34:1589. https://doi.org/10.1097/01.CCM.0000217961.75225.E9.

Luu A, Dominguez F, Yeshoua B, Vo C, Nallapa S, Chung D, et al. Reducing catheter-associated urinary tract infections via cost-saving diagnostic stewardship. Clinical Infectious Diseases 2021;72:e883–6. https://doi.org/10.1093/cid/ciaa1512.

Massis FD, Girolamo AD, Petrini A, Pizzigallo E, Giovannini A. Correlation between animal and human brucellosis in italy during the period 19972002. Clinical Microbiology and Infection 2005;11:632–6. https://doi.org/10.1111/j.1469-0691.2005.01204.x.
Schuetz P, Briel M, Christ-Crain M, Stolz D, Bouadma L, Wolff M, et al. Procalcitonin to guide initiation and duration of antibiotic treatment in acute respiratory infections: An individual patient data meta-analysis. Clinical Infectious Diseases 2012;55:651–62. https://doi.org/10.1093/cid/cis464.
Spellberg B. Principles of antibiotic therapy. vol. 1. 10th ed., 2025a, p. 218–28.
Spellberg B. Principles of antibiotic therapy. Mandell, douglas, and bennett's principles and practice of infectious diseases 10th edition, vol. 1. 10th ed., 2025b, p. 218–28.
Tamma PD, Avdic E, Li DX, Dzintars K, Cosgrove SE. Association of adverse events with antibiotic use in hospitalized patients. JAMA Internal Medicine 2017;177:1308–15. https://doi.org/10.1001/jamainternmed.2017.1938.
Theuretzbacher U. Pharmacokinetic and pharmacodynamic issues for antimicrobial therapy in patients with cancer. Clinical Infectious Diseases 2012;54:1785–92. https://doi.org/10.1093/cid/cis210.
Wald-Dickler N, Holtom PD, Phillips MC, Centor RM, Lee RachaelA, Baden R, et al. Oral is the new IV. Challenging decades of blood and bone infection dogma: A systematic review. The American Journal of Medicine 2022;135:369–379.e1. https://doi.org/10.1016/j.amjmed.2021.10.007.
Wald-Dickler N, Holtom P, Spellberg B. Busting the myth of "static vs. Cidal": A systemic literature review. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America 2017. https://doi.org/10.1093/cid/cix1127.
Yoshimura J, Yamakawa K, Ohta Y, Nakamura K, Hashimoto H, Kawada M, et al. Effect of gram stain–guided initial antibiotic therapy on clinical response in patients with ventilator-associated pneumonia: The GRACE-VAP randomized clinical trial. JAMA Network Open 2022;5:e226136. https://doi.org/10.1001/jamanetworkopen.2022.6136.