Gompf's Antibiotics Redux

A Pocket Tool for the Medical Student, or Resident on the Infectious Diseases Clinical Rotation
or
Just about anyone who could use a pocket antibiotic tool

By

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Made in the United States of America.

ANTIBIOTIC PEARLS

1. Penicillins generally cover Gram +s, anaerobes, certain Gram –s depending on the antibiotic.

2. Cephalosporins generally cover Gram +s (EXCEPT Enterococcus!), Gram –s, few or NO anaerobes. ONLY ceftazidime/cefepime cover Pseudomonas. They do not cover SPACEK/SPICE***** Gram negatives reliably; ceftriaxone/cefepime may be fine in less serious SPACEK/SPICE infections.

3. Aztreonam, a monobactam, covers ONLY Gram –s, incl. Pseudomonas. Reserve for beta lactam-allergic patients.

4. Aminoglycosides generally cover Gram +s (except tobramycin) & Gram –s, NO anaerobes, some Mycobacteria.

5. Quinolones cover Gram –s best (except moxifloxacin/delafloxacin, which are "respiratory quinolones" most active against Gram +s & anaerobes), some Mycobacteria.

6. Sulfas generally cover some Gram +s/MRSA, Nocardia, Listeria, Pneumocystis, most Gram –s except Pseudomonas.

7. Clindamycin generally covers Gram +s, incl anaerobes except Clostridia, like anaerobic/microaerophilic Strep/Peptostrep, Actinomyces (better for infections above the diaphragm).

8. Metronidazole generally covers anaerobes like Bacteroides, Prevotella, Clostridia; +/-Peptostrep (better for infections below the diaphragm).

9. Carbapenems are Big Gun Beta Lactams & Expensive. Use sparingly. Ertapenem covers most organisms except Pseudomonas. Imipenem, meropenem, & doripenem include Pseudomonas. Resistance in one carbapenem doesn't predict resistance in others.

10. A word about Enterococcus! Enterococcus in well-defined polymicrobial infections (cholecystitis, GI perforation, decubitus infections) tends to be somewhat of an opportunist & clears once source control is achieved, even if it spills into blood). Isolated Enterococcus faecalis/faecium bacteremia or hematogenous infection (septic arthritis, vertebral osteomyelitis, endocarditis, "community-acquired" bacteremia without an immediately source) should raise as much concern as Staphylococcus aureus. In that setting, even if reported as very ampicillin/penicillin-susceptible, and ampicillin is considered "drug of choice", know that these organisms have *lower*-affinity penicillin-binding proteins than other Gram + cocci, and "tolerance" may also occur with intermittent dosing of ampicillin/penicillin should be considered bacteriostatic. Synergistic combination therapy is preferred for these infections, such as amp + gentamicin. Amp + ceftriaxone/ceftaroline is increasingly preferred due to nephrotoxicity with gent & gent resistance. The combination of these beta lactams binds more PBPs that ampicillin alone & lowers the ampicillin MIC. In addition, know that vancomycin is bactericidal for most GPCs *except Enterococcus* (bacteriostatic).

Shameless plug:

Visit www.gompfsidpearls.net for more regularly updated ID clinical tools & links I find useful in practice. :}

Do's & DON'Ts

1. ***Don't use an antibiotic if you don't need to.***
   - ***If a bacterial infection is not high in the differential and the patient is not clinically toxic, forgo antibiotics. They are poor antipyretics.***
2. ***Persistent fevers require work-up, not more antibiotics.***
   If you are treating with broad antibiotics and fevers persist, ***stop them***; they aren't helping.
   - Look for undrained foci of infection/pus → drain it.
   - Look for non-infectious cause → treat it.
   - True FUO in a rapidly deteriorating patient may warrant empiric anti-TB therapy → Call ID.
3. ***DO use an oral antibiotic when you can; use one narrow antibiotic when you can; stop antibiotics when you can.***
   - Antibiotics are not cheap; switch to PO when reasonable.
   - Two antibiotics don't always prevent resistance better than one, and neither do broad spectrum drugs. More drugs = more resistance.
     - But NEVER give Rifampin alone! Rapid high-level resistance occurs.
     - TB/Atypical mycobacteria: *NEVER* use 1 drug in *active* TB
   - DON'T treat viral infections (or noninfectious syndromes) with antibiotics beyond the point at which you have ruled out bacterial infection.

4. ***Don't combine 2 of the same class of antibiotics (e.g. 2 beta lactams, 2 quinolones) unless you have data or your friendly neighborhood ID specialist to back it up. They may unpredictably antagonize, synergize, or double the adverse effects.*** E.g. Clindamycin-rifampin combo dramatically reduces clindamycin serum concentration***.***
   [https://doi.org/10.1016/j.jinf.2015.03.013; http://dx.doi.org/10.1684/ejd.2013.2213]

5. ***Always monitor for antibiotic adverse effects.***
   - Antibiotics are a double-edged sword. Respect them.
   - Watch for hypersensitivity/bone marrow suppression/interstitial nephritis/hepatotoxicity/drug fever with beta lactams, acute tubular necrosis/irreversible ototoxicity with aminoglycosides, & Clostridium difficile with almost all of them.
   - Watch for yeast overgrowth/Candidemia with prolonged/multiple antibiotic therapy.
   - C. diff. is easy to miss in 2 situations:
     - Colostomies – stumps/small bowel can be infected with C.diff.!
     - Spinal cord injured patients – unexplained abdominal distension & leukocytosis are a clue
   - RIFAMPIN REDUCES EFFECTIVENESS OF ORALCONTRACEPTIVES! Tell female patients to *add barrier contraception until the next new pill pack* after finishing antibiotics.

Antifungal coverage in general:

fluconazole = Cryptococcus, Coccidioides, dermatophytes, Candida EXCEPT Candida krusei/auris/some glabrata and all molds; high CSF/urine levels
itraconazole = Candida, Histoplasma, Crypto, Cocci, Aspergillus, Sporothrix, Paracocci, Talaromyces
voriconazole = Candida, Histo, Crypto, Aspergillus (except a few rare species, Fusarium, NOT initially for Mucor/Rhizopus, but OK as step-down after ampho B/source control; good CSF/poor urine levels
posaconazole = same as vori, + Mucor/Rhizopus; variable CSF levels
isavuconazonium 372mg (= isavuconazole 200mg) = same as posa, some Mucor, INFERIOR to caspofungin for *candidemia; few drug interactions; poor CSF/urine levels*
enchinocandins (caspofungin/micafungin/anidulafungin) = Candida incl C. auris, Aspergillus, SOME Cryptococcus, NOT Fusarium/Mucor/Rhizopus/Trichosporon, NOT Histo/Blasto/Coccidioides; poor levels in CSF/urine/vitreous humor
amphotericin B = all, +/- Fusarium, NOT Candida lusitaniae (variable)/guillermondi/auris, NOT Scedosporium (Pseudallescheria), Lomentospora (Scedosporium); Aspergillus terreus
flucytosine (5-flourocystosine) - increases penetration of above drugs, rapid resistance alone; good CSF/eye/urine levels

Fusarium: Vori 6mg/kg IV Q24H or 300mg PO x 1 d, then 4mg/kg/d IV or 200mg PO BID + Ampho B 1.2 mg/kg/d or ABLC 5mg/kg/d
Mucor: Ampho B 1.5mg/kg/d or liposomal ampho B or ABLC 5mg/kg/d + posaconazole/isuvaconazole (active metabolite of isuvaconazonium); NOT other azoles/enchinocandins

BacteriCIDAL vs. BacterioSTATIC
A consideration in choosing treatments for serious infection like severe sepsis, bacteremia, meningitis, pneumonia, endocarditis, neutropenic fever. A "cidal" drug kills quickly; a "static" drug slows or stops replication and/or toxic production. Whether it matters is somewhat controversial.

Beta lactams are CIDAL and penetrate tissues and inflamed meninges well. They are preferable in serious infection, including bacteremia, endovascular infection, CNS infection, and streptococcal cellulitis. Their microbial action is *time-dependent*, meaning that they are most effective the longer the concentration of drug in the affected site remains above the MIC of the bacteria. Thus, they can be dosed by *continuous or extended infusion*, which may also facilitate home & hemodialysis dosing. (UpToDate has a helpful chart; most drug databases like ePocrates, etc, don't offer alternative dosing recommendations.) Ceftazidime, cefepime, and ertapenem are stable enough to be given 3 times a week after hemodialysis. Ampicillin is stable at least 24 hrs for extended and continuous infusion.

Extended Spectrum Beta Lactamase (ESBL)-Producing Gram Negative Bacilli: It's complicated.

SPICE/SPACE/KEC are mnemonics for bacteria that either have *intrinsic* (chromosome-based, aka "constitutive") and/or *inducible* beta lactamases (chromosome- OR mobile genetic element/plasmid-mediated beta lactamases).
These organisms may *all* demonstrate resistance to commonly prescribed beta lactams and may require carbapenem* treatment. In addition, *inducible* beta lactamases may become reversibly de-repressed (or "switched on") upon 1- 7 days' exposure to a beta lactam and result in treatment failure.

Bottom Line Up Front: If suspecting sepsis, use ceftolozane-taz, ceftaz-avibactam, meropenem, or piperacillin-taz if MIC <16mg/L**; otherwise, can deescalate to cefepime if MIC ≤ 1 mg/L if stabilized.

KEC – Grouped by Family Enterobacteriaceae with moderate-high risk of ***inducible*, chromosomal beta-lactamase (AmpC, Group C, cephalosporinase)—KNOW that these may trick you by testing S to ceftriaxone/ceftazidime**, **→R may be induced**. Inducible beta lactamases may become reversibly de-repressed (or "switched on") upon 1- 7 days' exposure to a beta lactam and result in treatment failure. Cefepime is a weak AmpC inducer and stands up to hydrolysis by AmpC β-lactamase, so is generally a good choice if the organism is susceptible.

[Aside: Klebsiella pneumoniae & some E.coli often acquire a non-inducible, plasmid-based Group A beta lactamase (TEM) with a narrow spectrum against ampicillin & 1st-gen cephalosporins. Just be aware that this pattern comes up often in susceptibility testing & does not confirm or rule out an inducible ESBL.]

Klebsiella aerogenes (formerly Enterobacter)
Enterobacter cloacae
Citrobacter freundii

SPACE/SPICE – **Treat based on susceptibility report and severity.** [These species' ampC mutations are *usually not inducible*, so these DO test R to ceftriaxone/ceftazidime, so *this mnemonic has fallen out of favor*.] **Consider:** Severity of infection (bacteremia, meningitis), high inoculum/source control (UTI/pyelonephritis vs endocarditis), presence of biofilm (infected device), & MICs to cefepime (≤ 1 mg/L) & pip-tazobactam (≤ 16 mg/L)** can help guide whether to use cefepime, pip-taz, or a carbapenem. Quinolones (bactericidal), trimethoprim-sulfamethoxazole (TMP-SMX), tetracyclines, and aminoglycosides are options if susceptible.

Presence of **chromosomal ("constitutive", "intrinsic")** or **mobile genetic element-**acquired (**plasmid**-mediated) beta lactamases.
Serratia/**S**almonella/**S**higella
Proteus (non-P. mirabilis/"**I**ndole +")/**P**rovidencia
Pseudomonas
Acinetobacter baumanii complex
Citrobacter species
Enterobacter complex
(**Y**ersinia enterocolitica – not enough data)

E. coli and Klebsiella are the most common ESBL producers, so many labs screen those isolates if MIC for ceftazidime is >/= 2 mg/L. Remember that **Klebsiella** almost all have a constitutive chromosome-based beta lactamase (usually SHV-1) & test R to ampicillin/ticarcillin.

*Note that carbapenems and the monobactam, aztreonam *are* beta lactams, as they *all* have a beta lactam ring. This may be confusing initially when you read about beta-lactam resistance and recommendations to use a beta lactam "versus" carbapenem; many articles gloss over this.

**MERINO Trial 2018 suggested higher 30-day all-cause mortality with pip-taz vs meropenem, but other trials and post-hoc analysis of MERINO have suggested MIC > 16mg/L to pip-taz is responsible for the difference. If MIC is low, piperacillin-tazo may be acceptable as "carbapenem-sparing" in infections with source control (e.g. pyelonephritis without obstruction). See also Impact of the MIC of Piperacillin-Tazobactam on the Outcome of Patients with Bacteremia Due to Extended-Spectrum-Lactamase Producing Escherichia coli, 2013; Association Between Minimum Inhibitory Concentration, Beta-lactamase Genes and Mortality for Patients Treated With Piperacillin/Tazobactam or Meropenem From the MERINO Study 10/27/2020; IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 2.0, 3/31/2022.)

Carbapenem (CP) Resistant Gram Negative Bacilli:
(Carbapenem attached to the beta lactam ring is what preserves activity against ESBL.) Affects mainly **Klebsiella pneumoniae, Pseudomonas aeruginosa and Acinetobacter baumannii (CRAB)**. May possess intrinsic vs mobile genetic element carbapenemase-encoding genes that inactivate enzymes, induce efflux pumps or limit porin channels. Carbapenems are not necessarily interchangeable.

Antibiotics for Resistant Gram + Cocci

- Vancomycin, teichoplanin (Europe) cover all but vancomycin-resistant Gram +s.
- Vancomycin is bacterioSTATIC against Enterococcus.
- Dalbavancin, oritavancin, televancin - same mechanism as vancomycin & susceptibility generally correlates with vancomycin susceptibility; they add VRE, VISA/VRSA coverage.
- Daptomycin is bacteriCIDAL for both MRSA and Enterococcus & penetrates biofilm.
- Linezolid & tigecycline are bacterioSTATIC, NOT a choice for bacteremia unless no other options are possible, and not as monotherapy, unless you can cite legitimate supportive data.
- Tigecycline is difficult to tolerate due to 20% nausea/vomiting & associated with higher mortality than comparators for FDA-approved indications in after-market review of pooled clinical trials.
- All but vancomycin are EXPENSIVE & generally reserved for vancomycin-resistant Gram +s.

Pseudomonas, Acinetobacter, Stenotrophomonas vs other GNR

- These species are not of the family Enterobacteriaceae & often affect patients whose microbiome has been altered by extensive antibiotic/healthcare exposure.
- Acinetobacter are intrinsically resistant to multiple antibiotics and may be variably susceptible to carbapenems (*susceptibility to one carbapenem does not predict susceptibility to another!*).
- Stenotrophomonas are intrinsically resistant to carbapenemis; generally most susceptible to quinolones, sulfas, and tetracyclines.

Which antibiotics are bacterioSTATIC?

"In sepsis, restore **V**olume with a **L**iter of **NM**L (normal) **S**aline."

Vancomycin in Enterococcus; cidal for all other GPCs
Linezolid/**L**efamulin
Tetracyclines/**T**igecycline
Nitrofurantoin
"MLS antibiotic group" – clindamycin, macrolides (Note: streptogramins are bactericidal)
Sulfas/trimethoprim

Everything else is bactericidal.
Note bene: Clindamycin is used as an *adjunct* for Staph or Strep toxic shock, severe streptococcal cellulitis or suspected necrotizing infection; it *halts protein synthesis*—i.e stops production of toxins that mediate severe inflammation, necrosis, and toxic shock. Many Staphylococcus aureus strains carry *inducible* clindamycin resistance genes, so I suggest having susceptibilities available before relying on clindamycin alone for this pathogen (if your lab doesn't report inducible clindamycin resistance, check for erythromycin resistance---*erm* mutation! ---as a clue). You can also use other drugs whose mechanism of action is disruption of protein synthesis: linezolid, doxycycline/minocycline/tigecycline for toxin-inhibition in severe Staph infection.

What does the MIC mean & how do we use it?

The MIC is the lowest concentration of an antimicrobial agent that completely prevents visible growth of the test strain of an organism in culture. Each antibiotic will have a different MIC for each organism. The MIC value of an antibiotic must be compared with clinical outcomes for the disease caused by a given organism; in some cases, this is further drilled down to differentiate between clinical scenarios (e.g., meningitis vs UTI), and the pharmacokinetics of individual antimicrobials. This overview yields "*clinical breakpoints*" that define whether the strain is susceptible (S), susceptible dose dependent (SDD) or resistant (R) to the antibiotic. Clinical breakpoints are internationally reviewed & and adjusted yearly according to expert consensus, epidemiology, and clinical literature by EUCAST (European Committee on Antimicrobial Susceptibility Testing), the American CLSI (Clinical and Laboratory Standards Institute), and further updated by the FDA (Food and Drug Administration). Fortunately, your friendly hospital Micro lab and their automated systems do a LOT of the interpretation work for you. If Micro says it's susceptible, it usually is—just beware of SPICE/CEK (☝). And vancomycin "MIC creep" with S. aureus bacteremia—as MIC "creeps" above 1, so does treatment failure. Etc, etc.

Pharmacokinetics & Pharmacodynamics (PK/PD)

Important determinants of antibiotic dosing for maximal effect include time-dependent vs concentration-dependent activity, volume of distribution/Vd (obesity, serum albumin), and route of elimination (renal, hepatic [cytochrome P450 enzymes], GI).

Time-Dependent antibiotics depend on duration of time that free antibiotic levels remain in tissue above MIC, no post-antibiotic effect. Doses must be given at regular intervals to maintain activity. Low albumin levels may lower free antibiotic levels by allowing increased free antibiotic to be cleared before it gets into tissues (highly protein-bound antibiotics may need higher doses, esp with less susceptible organisms).

- All beta lactams, monobactam, carbapenems

Concentration-dependent antibiotics act by achieving a high initial concentration & have a persistent "post-antibiotic effect"—i.e. bacterial growth is inhibited or "stunned" for a long time even after concentrations are no longer above MIC. Allows for extended dose intervals. Low albumin levels may lower free antibiotic levels by allowing increased free antibiotic to be cleared before it gets into tissues. At higher doses, highly protein-bound antibiotics may maintain adequate serum concentration if enough free antibiotic is available; again, may need higher dose).

- Aminoglycosides
- Daptomycin
- Metronidazole
- Quinolones (mostly)

Combination of Time above MIC + Post-antibiotic Effect

- MLS group – macrolides, clindamycin, tetracyclines
- Linezolid
- Vancomycin – dosing is optimized by achieving certain concentration for certain period of time, or "area under the curve" (AUC) -based dosing

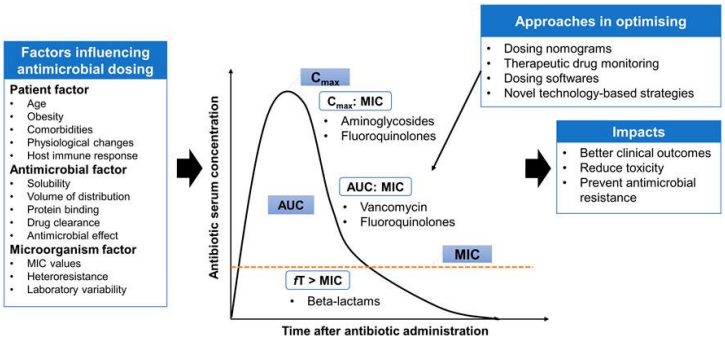

Table I. Protein binding of antibacterials commonly used in critically ill patients and of antibacterials in development (all protein binding data have been adapted from Donnelly et al.[26] and MIMS Australia[27]). We have also included data on antifungal agents for the reader's reference

Highly bound (>70%)	Moderately bound (70–30%)	Minimally bound (<30%)
Amphotericin B (90%)	Azithromycin (7–51%)	Amikacin (0–11%)
Anidulafungin (>99%)	Aztreonam (60%)	Amoxicillin (17–20%)
Caspofungin (97%)	Cefotaxime (40%)	Ampicillin (15–25%)
Cefazolin (75–85%)	Cefuroxime (33–50%)	Cefepime (16–19%)
Cefonicid (98%)	Cephalothin (55–75%)	Ceftazidime (17%)
Cefoperazone (90%)	Ciprofloxacin (20–40%)	Ceftobiprole (22%)
Cefoxitin (80–50%)	Clarithromycin (42–50%)	Cefpirome (9%)
Ceftriaxone (85–95%)	Chloramphenicol (60%)	Colistin (<10%)
Clindamycin (90% bound to α_1-acid glycoprotein)	Levofloxacin (50%)	Doripenem (8%)
Cloxacillin (94%)	Linezolid (31%)	Ethambutol (20–30%)
Dalbavancin (93%)	Moxifloxacin (30–50%)	Fluconazole (11–12%)
Daptomycin (90–93%, 30% to α_1-acid glycoprotein)	Nitrofurantoin (40%)	Fosfomycin (0%)
Dicloxacillin (97%)	Benzylpenicillin [penicillin-G] (65%)	Gentamycin (<30%)
Doxycycline (93%)	Piperacillin (30%)	Imipenem (20%)
Ertapenem (85–95%)	Sulfamethoxazole (68%)	Isoniazide (0–10%)
Erythromycin (73–81%)	Ticarcillin (55%)	Meropenem (2%)
Faropenem (96–99%)	Trimethoprim (45%)	Metronidazole (<20%)
Flucloxacillin (95%)	Vancomycin (30–60%)	Norfloxacin (10–15%)
Fusidic acid (95–97%)	Voriconazole (58%)	Polymyxin B (<10%)
Iclaprim (93%)		Quinupristin/dalfopristin (11–26%)
Itraconazole (99.8%)		Tobramycin (<30%)
Lincomycin (80–90%)		
Minocycline (75%)		PO cefpodoxime (18-30%)
Nafcillin (90%)		
Oxacillin (93%)		
Posaconazole (>97%)		
Rifampicin [rifampin] (80%)		
Sulfisoxazole (92%)		
Teicoplanin (90–95%)		
Telavancin (92–94%)		
Tigecycline (71–89%)		

THE CLASSES (not an exhaustive list)

Penicillins – beta lactams are CIDAL, good tissue penetration

DRUG	COVERAGE	USES	TOXICITY	Cerebral Spinal Fluid (CSF)
penicillin G $ CIDAL	Group A Strep (no resistance) Strep viridans Neisseria Capnocytophagia Actinomyces Fusobacterium Clostridia perfringens/tetani Pasteurella Treponema/ Leptospirosis NOT Staph aureus (resistant)	Skin/soft tissue (SST) or mouth infections	Hypersensitivity Stevens Johnson Interstitial nephritis Seizures (if high level) Bone marrow suppression C.difficile	YES if inflamed
AminoPCN $$ amoxicillin* ampicillin* amox/clav amp/sulbactam CIDAL	Add to the above: Listeria MSSA Most Pneumococcus Proteus Hemophilus influ. (beta lactamase negative) Salmonella/Shigella Anaerobes * *Klebsiella are intrinsically resistant to amp/amox* (clavulanate/sulbactam don't add much activity) Note: High-dose amp-sulbactam may used as a source of *sulbactam* in treating MDR Acinetobacter	Otitis media Sinusitis SST Meningitis in elderly	Above	
CarboxyPCN $$ ticarcillin/clav (Europe) piperacillin piperacillin/tazobactam CIDAL	Adds to the above: Pseudomonas Enterobacteriaceae* Stenotrophomonas (ticar) Gut anaerobes MSSA Pip & Pip/tazo more potent for GNRs & more resistant to AmpC/ESBLs (See "SPICE" above) **Klebsiella is intrinsically R to ticarcillin*	Adds to above: Gut/ surgical infections Nosocomial pneumonia Prostate Osteomyelitis	Above	

Cephalosporins – Think of progressive broadening of spectrum from Gram + to Gram - with each generation. Beta lactams are CIDAL. [☺= can be dosed 3 times weekly in dialysis patients] ***CROSS-ALLERGY (same side chains) between aztreonam – ceftazidime – cefiderocol***

DRUG	COVERAGE	USES	TOXICITY	CSF

1st Generation $$ cephalexin PO cefadroxil PO cefazolin IV/IM ☺ CIDAL	GPC/MSSA/streptococci, E. coli, Proteus, some Klebsiella (increasingly ampC+/ESBL) NOT Enterococci	SSTI Uncomplicated/Non-diabetic osteomyelitis PreOP prophylaxis	Hypersensitivity Bone marrow suppression Diarrhea C.difficile	POOR
2nd Generation $$ cefuroxime (IV/PO) cefaclor (PO) Cefamycins: cefoxitin (IV) cefotetan (IV)	Streptococci, uncomplicated MSSA Pneumococcus Neisseria Some GNR except Pseudomonas **Cefamycins are the only ones that reliably cover *anaerobes*** NOT Enterococci	Community acquired pneumonia (CAP) meningitis OM/sinusitis Gonorrhea	Hypersensitivity RASH/Stevens Johnson w/ cefaclor High INR/PT w/ cefoxitin/ cefotetan Bone marrow suppression C.difficile	YES if strongly inflamed -- ceftriaxone >90% protein bound, low BBB penetration
3rd Generation $$ Cefpodoxime (PO) ceftriaxone (IM/IV, QD dosing) cefotaxime (IV) CIDAL	Above; covers viridans streptococci, pneumococcus, but reduced PBP binding in MSSA	Meningitis CAP Most community-acquired infections Gonorrhea Pyelonephritis Best *PO* ceph for GU is cefpodoxime (20-30% protein-bound, vs PO cefdinir, which is poorly excreted in urine & up to 70% protein-bound)	Above Ceftriaxone: *Pseudocholelithiasis* (biliary sludge)	
4th Generation/Anti-pseudomonal $$ ceftazidime (IV) ☺ cefepime ☺ CIDAL	Above, plus Pseudomonas More resistant to beta lactamases/ESBLs (See "SPICE" above) because it is not porin-dependent NOT Enterococci	Above, plus neutropenic fever	Above Cefepime: *Encephalopathy*, non-convulsive status epilepticus	

5th Generation/Anti-MRSA $$$ ceftaroline CIDAL	Similar to 3rd generation, plus MRSA, VISA/VRSA/VRE faecalis (NOT E. faecium), pneumococcus, beta-lactamase + H.flu, Moraxella Listeria NO Pseudomonas	Complicated SSTI, CAP (NOT MRSA-insufficient data)	Above	
Advanced-generation/Anti-pseudomonal ceftolozane-tazobactam ceftazidime-avibactam CIDAL	Viridans streptococci NOT Enterococci or Staphylococci ceftoloz-taz covers GNRs incl Pseudomonas, ESBLs, *some* carbapenemase-producing P. aeruginosa (CRPA), NOT KPC+ ceftaz-avi covers ESBL & KPC+ carbapenemase (1st line agent) ceftaz-avi covers GNRs incl Pseudomonas, adds coverage for ceftaz-R, ESBLs, some ampC-R, *some* carbapenemases (NOT metallobetalactamase)	Complicated UTI/pyelo Complicated intraabdominal infection ceftaz-avi adds HAP	Above Nausea, diarrhea, headache, fever, renal insufficiency (ceftolaz-taz)	ceftazidime -- CSF: YES if inflamed (NOT avibactam) -- 90% renal excretion, unchanged (avibactam 97%) -- < 10% protein bound ceftolozane -- CSF UNKNOWN -- > 95% renalexcretion, unchanged -- 30% protein bound
cefiderocol CIDAL Similar side chains of both cefep & ceftaz Trojan horse siderophore: Chelates Fe++, so drug is actively transported with Fe++ via siderophore channels	Reliably covers XDR/carbapenem-R: *Metallobetalactamase* producers (MBL) Klebsiella pneumoniae (KPC+) Pseudomonas aeruginosa (CRPA) Enterobacteriaceae (CRE) Acinetobacter baumanii (CRAB) Stenotrophomonas Burkholderia cepacian NO GPC!	Complicated UTI/pyelo HAP	Hypersensitivity Bone marrow suppression Diarrhea C.difficile Unclear if higher all-cause mortality in critically ill with carba-R GNB (CREDIBLE-CR trial)	-- CSF POOR -- 58% protein bound -- 60-70% renal excretion, unchanged

Monobactam

DRUG	COVERAGE	USES	TOXICITY	CSF
aztreonam $$ CIDAL	ONLY GNRs, incl Pseudomonas Covers metallobeta-lactamase car-bapenemases, but not ESBL (resistance usually occurs to-gether)—combination of aztreonam + ceftaz-avibactam might be used in salvage cases (CID 2021;72:1871)	GNR infections; NOT a replacement for all aminoglyco-side uses (no syn-ergy for GPC, NO Enterococcal cov-erage)	Low Good alternative for beta lactam allergies EXCEPT with ceftazidime, cefiderocol	YES if in-flamed [Modal J et al. AAC. 1986;29:281-3.]

Carbapenems (Reserved for Multidrug Resistant Organisms – MDRO)
[☺= can be dosed 3 times weekly in dialysis patients]

DRUG	COVERAGE	USES	TOXICITY	CSF
imipenem-cilastin meropenem meropenem-vaboractam imipenem-cilastin-relebactam $$$	GPCs EXCEPT MRSA GNRs EXCEPT Stenotrophomonas/Burkholderia ESBL+ & "SPICE" GNRs Anaerobes (incl Cutibacterium) Listeria Pneumococcus Nocardia asteroides (NOT brasiliensis) Legionella Mycobacterium avium Enterococcus (NOT E. faecium) mero-vaboractam adds *carbapenemase+ Klebsiella pneumonia (KPC)*, class A carbap-R Enterobacteraciae (NOT metallobetalactamase/OXA carbap-R, NOT carbap-R Pseudomonas/Acinetobacter) Relebactam is not active against Morganellacea group (Morganella, Proteus, Providentia)	Resistant GNR infections Serious gut infections Necrotizing pancreatitis	IV/IM Hypersensitivity (~10% cross-allergy with beta lactams) Seizures with imipenem (if renal insufficiency or high levels used) Candida overgrowth/ infections C.difficile	YES
doripenem $$$ CIDAL	Above, possibly lower MICs to Pseudomonas & Acinetobacter	Above Higher mortality than imipenem in VAP	Above	
ertapenem ☺ $$$ CIDAL	Above, without Pseudomonas coverage	Postpartum uterine infections Postsurgical Abdominal infections (not Pseudomo-nas)	Above *Encephalopathy*	

Aminoglycosides

DRUG	COVERAGE	USES	TOXICITY/ MISC	CSF
gentamicin streptomycin spectinomycin tobramycin amikacin liposomal amikacin $-$$$ CIDAL	Gent: VSE/VRE/variable Staph, GNRs incl Pseudomonas Tobra/Amik: GNRs incl Pseudomonas Amik: TB, non-TB Mycobacteria Strepto -Yersinia -MDR Mtb Gent/Strepto -Tularemia Spectino -Gonorrhea NO coverage for: Acinetobacter/Stenotrophomonas Anaerobes Pneumococcus	Synergy with beta lactams for GPC/Pseudomonas infections Usually not used alone except for UTIs	IV/Aerosol Acute tubular necrosis (reversible) Cochlear toxicity (genetic predisposition) Vestibular toxicity (irreversible) When possible: -stop after 3-5 d -use once-daily dosing -avoid in elderly Liposomal amik – hypersensitivity pneumonitis, hemoptysis, bronchospasm, exacerbation of lung disease Neuromuscular blockade (may exacerbate myasthenia gravis & paralytic agents)	NO or UNKNOWN (use intrathecal)
fosfomycin $$ CIDAL	Enterococcus Staph. aureus GNRs	Simple cystitis in women Off-label q3days for complicated or MDR GNRs, VRE if susceptible	PO only Above, significant diarrhea	
plazomicin $$ CIDAL	GNRs incl MDR/KPC/metalobetalact/CRE GNRs,variable Pseudomonas (use only if known susceptible), NOT Steno, Acinetobacter	Complicated UTI/pyelo	IV only Above Limited data	

Sulfonamides/Sulfas (*INTRACELLULAR* ACTIVITY)

DRUG	COVERAGE	USES	TOXICITY/MISC	CSF
trimethoprim-sulfamethoxazole co-trimoxazole $ STATIC for Staph	Staph. aureus (incl MRSA) *(NOT Enterococcus, Pseudomonas, Acinetobacter)* *Legionella* *Stenotrophomonas* *Listeria* *Pneumocystis* *Nocardia* Burkholderia cepacia Moraxella Yersinia Francisella tularensis *Toxoplasma* Atypical mycobacteria (*M. marinum*) Some common coliforms	UTI MRSA SSTI Specific agents at left	IV/PO RASH/Stevens Johnson Nausea Fever Bone marrow suppression Hemolysis (if G6PD deficient) Hepatotoxicity Elevated creatinine or K+ (competes with Cr for tubular secretion, blocks K+ excretion) Kernicterus in neonates C.difficile Sun sensitivity	YES

Pleuromutilins (*INTRACELLULAR* ACTIVITY)

DRUG	COVERAGE	USES	TOXICITY/MISC	CSF
Lefamulin** IV/PO Protein synthesis inhibitor – multiple binding sites to ribosome, higher resistance barrier STATIC	S. pneumoniae MSSA, ?MRSA Hemophilus influenzae Mycoplasma pneumoniae Chlamydia pneumoniae Legionella pneumophila	CAP/community-acquired pneumonia ** Bacteriostatic – be aware of this when empirically treating serious infections.	Nausea, hepatotoxicity, CNS Hypokalemia Prolonged QTc Teratogenicity C. difficile	UNKNOWN 70% fecal excretion

Macrolides/Lincosamides (Macrolide-Lincosamide-Streptrogramin B class, or MSL—all bind 50s ribosome subunit & share resistance genes)

DRUG	COVERAGE	USES	TOXICITY/MISC	CSF
Macrolides erythromycin clarithromycin azithromycin $$ STATIC	Pneumococcus IF local resistance is <25% MSStaph. aureus (not MRSA) Legionella Listeria Hemophilus Moraxella Mycoplasma *Pertussis* Neisseria meningitis Chlamydia/Hemophylus ducreyi Campylobacter Helicobacter pylori Salmonella/Shigella *Bartonella* Borrelia burgdorpheri (*Lyme* disease *Babesia* microti Actinomyces Atypical mycobacteria	LRTI/ bronchitis Sinusitis Dental/ oral infec-tions Atypical mycobacteria (incl MAC prophy in HIV)	IV/PO Nausea/ vomiting Abdominal cramps/ diarrhea (Lowest with Azithro) C.difficile Ototoxicity with chronic use Rare association with cardio-vascular mortality with QTc prolongation, low Mg++/K+. Interactions: Ery/Clari induce P450! Neuromuscular blockade with Ery (may exacerbate myas-thenia gravis & paralytic agents)	Adequate – better for Mycoplasma, Legionella, Chlamydia

<u>Lincosamides</u> clindamycin $$ STATIC	CIDAL for Group A streptococcus, MSStaph. aureus (MRSA, but watch for inducible *erm* resistance. Clue is resistance to erythro-mycin) Pneumococcus Inhibits toxic proteins in severe Strep A & S. aureus/ necrotizing fasciitis. Oral anaerobes: Gram + such as Peptostrep-to-coccus, Fusobacterium, Prevotella, Actinomyces, & Clos-tridial spp other than Clostridium difficile Gram – such as Bac-teroides (may not cover in up to 25% of cases or strains with MIC >/= 8 mcg/mL) Babesiosis	Severe SSTI, necrotizing fasciitis, MRSA *"Infections above the diaphragm"* Head and neck/dental infections Lung ab-scess/ aspiration pneumonia (*tip: no teeth = no anaero-bes*) Bacterial vaginosis Babesiosis Toxoplasma in HIV	IV/PO <u>C.difficile!!</u> (>30% develop it on a week of clinda) Dysgeusia Rash, fever, eosinophilia Erythema multiforme Reversible neutro-penia/thrombocytopenia Watch for hepatitis/obstructive jaundice, severe liver injury Neuromuscular blockade (may exacerbate myasthenia gravis & paralytic agents)	POOR except for Toxoplasmosis in HIV

Nitrofuran

DRUG	COVERAGE	USES	TOXICITY/MISC	CNS
nitrofurantoin $ CIDAL	GNRs EXCEPT Pseudomonas, Proteus, and Enterococcus incl susceptible VRE Multiple sites of action, inhibits synthesis of DNA, RNA, proteins, cell wall – higher resistance barrier than most antibiotics	Cystitis Susceptible ESBL GNRs ONLY reaches therapeutic level in URINE	PO only Nausea/ vomiting C.difficile	NONE

Quinolones (Resistance is rising due to overuse; single-step mutation→ resistance may arise *while on therapy*; *INTRACELLULAR* ACTIVITY; high concentration in bone, prostate, CSF)

DRUG	COVERAGE	USES	TOXICITY/MISC	CSF
"Gram negative" Quinolones ciprofloxacin levofloxacin norfloxacin $-$$ CIDAL	GNRs including Pseudomonas Levo covers pneumococcus & Stenotrophomonas well "Atypical" pneumonia: Mycoplasma, Chlamydia, Moraxella Some mycobacteria/TB	UTI/GU infection Intraabdominal infections Endometritis Hospital-associated lung infections Levo best for acute sinusitis/ CAP Norflox: UTI only	IV/PO *IV=PO (bioequivalent)* Dizziness/CNS Diarrhea Hypo-/hyperglycemia Sun sensitivity May exacerbate myasthenia gravis & paralytic agents (inhibits GABA receptors) May prolong QTc (watch for palpitations/syncope; avoid if QTc > 500msec, cardiomyopathy) Rare spontaneous tendon rupture (watch for pain at tendon sites) *Aortic dissection association* C.difficile	YES, HIGH DOSE
"Gram positive or Respiratory" Quinolone moxifloxacin $$ CIDAL	Pneumococcus, Streptococci, Staphylococcus (NOT MRSA) Legionella Gut anaerobes Atypical myco-bac/TB	CAP/community-associated respiratory infections Acute sinusitis Intraabdom-inal infections SSTI	IV/PO *IV=PO (bioequivalent)* Above >60% *liver* excretion	UNKNOWN
"Gram positive or Respiratory" Quinolone delafloxacin $$ CIDAL	Streptococci, Staphylococcus *MRSA* Pseudomonas Legionella Gut anaerobes Atypical myco-bac/TB	SSTI CAP/community-associated respiratory infections	IV/PO *IV=PO (bioequivalent)* Above	UNKNOWN

Nitroimidazole

DRUG	COVERAGE	USES	TOXICITY/MISC	CSF
metronidazole $$	Gram – anaerobes incl. Bacteroides fragilis and all Clostridia	*"Infections below the diaphragm"* Intraabdominal abscess, peritonitis,	IV/PO Disulfiram-like reaction (vomiting) if ethanol	YES

CIDAL	Entamoeba coli	diverticulitis, etc Endometritis/ Bacterial vaginosis Clostridium difficile colitis Entamoeba liver abscess/ dysentery NOT to be given alone for lung abscess/ENT infections	consumed within 3 days of therapy Aseptic meningitis/ neuropathies, rare	

Tetracyclines/Glycylcycline (*INTRACELLULAR* ACTIVITY)

DRUG	COVERAGE	USES	TOXICITY/MISC	CSF
Tetracyclines Minocycline Doxycycline $ STATIC	**MRSA**/MSSA Pneumococcus, +/- GAS E. coli Legionella N. meningitidis Hemophilus Moraxella Mycoplasma Chlamydia Listeria Brucella Actinomyces Borrelia burgdorferi Rickettsia Vibrio Treponema Anaerobes: Fusobacterium, Cutibacterium, Peptostreptococcus, Clostridium, some Bacteroides fragilis/melanogenicus	Acne/rosacea SSTI CAP, esp under age 40 Dog/cat bite prophy as alternative to amox/clav Tickborne diseases	IV/PO Discoloration of permanent teeth in children Esophageal ulcer Hepatotoxicity Pseudotumor cerebri, esp minocycline! (watch for headache) Sun sensitivity C.difficile Inhibit lipopolysaccharide-induced proinflammatory products	YES (neurobo-relliosis, syphilis)
Glycylcycline tigecycline ǂ** $$ eravacycline* omadacycline sarecycline (acne only) STATIC	Above, plus Staph. epidermidis Enterococci Corynebacterium N. gonorrhea ESBL + E.coli/Klebs (NOT KPC) Stenotrophomonas Acinetobacter Salmonella B. fragilis/ anaerobes Clostridia incl. C.difficile NOT Pseudomonas, Burkholderia *eravacycline adds ESBL, carbap-R Acinetobacter	SSTI Intraabdo-inal infections CAP/HAP Severe C.difficile Y alveolar, soft tissue, bile/gut entry Poor bone/joint, CNS ** Bacteriostatic – be aware of this when empirically treating serious infections. ǂ **Increased mortality** vs. comparators in after-market review of pooled clinical trials, incl in FDA-approved indications.	IV only Above 20% tige, 6.5% erava - nausea, vomiting Inhibit lipopolysaccharide-induced proinflammatory products */** Ampicillin/ Amoxicillin CIDAL-preferred in VRE that is amp-susceptible.	UNKNOWN

Glycopeptides, lipoglycopeptides

DRUG	COVERAGE	USES	TOXICITY/ MISC	CSF
vancomycin $ CIDAL except *STATIC for Enterococci*	Gram + cocci except VRE/VRSA *Most* Gram + rods (but see below) Corynebacterium Listeria C.diff (only PO) Increasing vancomycin MICs > 1 assoc with treatment failures ("MIC creep") **Instrinsic resistance in:** Leuconostoc Lactobacillus Propionobacterium Pediococcus Erysipelothrix Clostridia(non-diff.)	SSTI due to MRSA HAP/CAP due to MRSA Infections due to VRE	Vanc IV≠PO – PO not absorbed from gut Vanc requires a **central IV line**, due to phlebitis (which may cause fevers, unnecessary antibiotics/cultures/increased lengths of stay…) "Red man syndrome" with vanc (histamine release) if infused too rapidly—infuse over 1-2 hours Leukopenia Thrombocytopenia Rare interstitial necrosis Ototoxicity (abrupt, irreversible, usually elderly) Rarely, DRESS	YES
dalbavancin $$$	MSSA, MRSA, Group A, B streptococci, Strep anginosus group	SSTI, osteomyelitis/prosthetic joint infection, endocarditis, bloodstream infection 1500mg IV x1 OR 1000mg IV then 500mg in 7 days	Nausea, headache, diarrhea Hepatotoxicity "Red man syndrome" with vanc (histamine release) if infused too rapidly—infuse over 1-2 hours	
televancin $$$	MSSA, MRSA/VISA/VRSA, Group A, B streptococci, Strep anginosus group, VSEnterococcus	SSTI HAPneumonia due to MRSA/VISA	N/V, foamy urine Nephrotoxicity QTc prolongation Mortality > with mod/sev renal impairment compared with vanco Possibly teratogenic—avoid in pregnancy unless maternal benefit exceeds fetal risk "Red man syndrome" with vanc (histamine release) if infused too rapidly—infuse over 1-2 hours	

			Interferes with coag tests but not coagulation	
oritavancin $$$ CIDAL including *Enterococci*	MSSA, MRSA, Group A, B, C streptococcus, Streptococcus anginosus group, VSEnterococcus	SSTI **FAILED for osteo-myelitis** 1200mg IV x1, over 3 hr	Headache, N/V "Red man syndrome" with vanc (histamine release) if infused too rapidly—infuse over 1-2 hours Hepatotoxicity Artificially prolong PT/INR for up to 12 hr (5.1); aPTT for up to 120 hours, and may prolong PT and INR for up to 12 hr and ACT for up to 24 hr—Use Factor Xa assay for coagulation testing Coadministration with warfarin may result in higher exposure of warfarin and increase risk for bleeding; monitor frequently for signs of bleeding	

Cyclic Lipopeptides

DRUG	COVERAGE	USES	TOXICITY/ MISC	CSF
daptomycin $$$$ CIDAL	All Gram + cocci incl. Vanc-/Amp-resistant* Entero-coccus MRSA/VRSA	SSTI Bacteremia Osteomyelitis, Joint infections May be active in biofilms (which usually inactivate antibiotics)	IV only False Prothrombin Time prolongation Nausea/vomiting Rhabdomyolysis & associated renal insufficiency (weekly creatinine, CPK) Rare asthmatic pul-monary eosinophilia NOT for primary pneumonia because it is inactivated in alveolar fluid, BUT seems effective in embolic lung infec-tion/septic emboli due to Gram +s, since the infection is more parenchymal. *ampicillin/ amoxicillin (CIDAL) preferred in VRE that is amp-susceptible.	UN-KNOWN

Streptogramins

DRUG	COVER-AGE	USES	TOXICITY/ MISC	CSF
~~quinupristin-dalfopristin~~ ~~$$$$~~ ~~CIDAL~~ Discontinued by Pfizer 2022	~~Vanc-/Amp-resistant*~~ ~~Enteroco-ccus faecium~~ ~~MSSA~~ ~~Group A Strep~~ ~~NOT Entero-co-ccus fae-calis or MRSA~~	~~SSTI/non-MRSA~~ ~~Bacteremia~~ ~~Endocarditis due to VRE faecium~~ ~~Extremely limited use.~~	~~IV only~~ ~~Needs~~ **~~central IV line due to frequent pain, phlebitis, fever~~** ~~>30+%~~ **~~Myalgias/ Arthralgia~~**~~s~~ ~~Nausea/~~ ~~Vomiting/~~ ~~Diarrhea~~ ~~*ampicillin/ amoxicillin (CIDAL) preferred in VRE that is amp-susceptible.~~	~~UNKNOWN~~

Oxazolidinone (*INTRACELLULAR* ACTIVITY)

DRUG	COVER-AGE	USES	TOXICITY/ MISC	CSF
linezolid $$$$ STATIC except CIDAL for streptococci	All Gram + cocci incl. ** vanc-/amp-resistant* Entero-coccus MRSA/VRSA TB/Atypical myco-bacteria Binds 23S rRNA-blocks formation of 50s/70s ribosomal initiation complex	SSTI MRSA HAP/CAP due to MRSA Osteomyelitis/ Joint infections (good bone pene-tration) **NOT for bactere-mia without a well-defined and remov-al or draining focus, NOT for endovas-cular infections	*IV=PO (bioequivalent)* Nausea/ vomiting/ diarrhea Temporary tooth staining Headache Thrombocytopenia/ Neutropenia after 7 days Peripheral/ Optic neuropathies with extended use Lactic acidosis (nausea, fatigue) **Serotonin syndrome:** Avoid high tyramine food/drink, SSRIs (> 100mg tyramine per meal). E.g. aged cheeses, dried/processed meats, ethanol, sauerkraut, soy sauce, or yeast ex-tract/supplements, fer-ments */**ampicillin/amoxicillin (CIDAL) preferred in VRE that is amp-susceptible. **Associated **with treat-ment failure in bactere-mia**, incl line & endovascu-lar infections.	GOOD Myrianthefs et al. Serum and CSF concentrations of linezolid in neurosurgery patients. AAC 2016. 50(12): 3971-6.
tedizolid $$$$ STATIC	All Gram + cocci incl. ** VRE, Amp-resistant* Entero-coccus, MRSA/VRSA Binds 50s riboso-mal subunit	SSTI	*IV=PO (bioequivalent)* 6 days tedizolid Qdaily = 10 days linezolid BID = higher lipid solubility/higher tissue levels Nausea/headache/diarrhea Lower thrombocytopenia than linezolid; similar neuropathic events; no longer term data **Serotonin syndrome:** Avoid high tyramine food/drink (> 100mg tyramine per meal). E.g. aged cheeses, dried/processed meats, ethanol, sauerkraut, soy sauce, or yeast ex-tract/supplements, fer-ments	NO DATA – suspect similar to linezolid

Colistin/Polymixin B (Reserved for multi-drug resistant organisms - MDRO)

DRUG	COVERAGE	USES	TOXICITY/MISC	CSF
colistin polymixin B colistimethate $$$ CIDAL	Gram - including Pseudomonas, Acinetobacter membrane disruption, binds lipopolysaccharide (LPS)/ Gram - endotoxin	Intraabdominal infections UTI/GU infections Pneumonia/ Hospital-associated respiratory infections Potent anti-LPS binding/ neutralizing activity	IV/Aerosol 30% Nephrotoxicity! Peripheral/ Optic neuropathies Neuromuscular blockade (may exacerbate myasthenia gravis & paralytic agents)	YES

Rifamycins

DRUG	COVERAGE	USES	TOXICITY/MISC	CSF
rifampin $-$$ Only rifampin is discussed here, in context of use outside of mycobacterial infections CIDAL	Very broad, incl GPC/GNR, mycobacteria; use is *condition*-specific RAPID RESISTANCE if given alone – *Use in combinations* Inhibits DNA-dependent RNA polymerase	*Only* used alone as prophylaxis against Neisseria meningitidis (2 days), Hemophilus influenza b (4 days) in contacts/nasal carriage Combination treatment in serious S. aureus, Streptococcal infections Combination treatment of Legionella, Anthrax, Brucella, Bartonella, Anaplasma, Ehrlichia Combination treatment of tuberculous and non-tuberculous Mycobacteria	IV/PO Red urine, sweat, tears, saliva – hold soft contact use Nausea, abd pain Hepatotoxicity (avoid ethanol & hepatotoxins), hyper-bilirubinemia Type I & Flu-like hypersensitivity Autoimmune reactions Many drug interactions – always check an updated reference	YES

References:

https://pubmed.ncbi.nlm.nih.gov/

http://webedition.sanfordguide.com/

www.drugs.com

www.emedicine.medscape.com

www.epocrates.com

www.micromedix.com

Ulldemolins M, Roberts JA, Rello J, Paterson DL, Lipman J. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. Clin Pharmacokinet. 2011 Feb;50(2):99-110. doi: 10.2165/11539220-000000000-00000. PMID: 21142293.

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Thank YOU, dear Colleague, for your dedication to the Art and Science of Medicine.
I hope that you find this tool of help in your care of the VIP at the center of our efforts:

The Patient.

Dr. G