

Antimicrobial Fundamental Concepts

Pharmacodynamics and Therapeutic Drug Monitoring

Pharmacokinetics versus pharmacodynamics

Pharmacokinetics mathematically describe the relationship of antibiotic concentration to time. Terminology that is typically associated with pharmacokinetics includes: absorption, distribution, metabolism, elimination, half-life, volume of distribution, and area under the concentration-time curve (AUC).

Pharmacodynamics describe the relationship of antibiotic concentration to pharmacologic effect or microorganism death. The three main pharmacodynamic parameters that are used are the peak to minimal inhibitory concentration ratio (peak/MIC), the AUC to MIC ratio (AUC/MIC), and the time the drug concentration remains above the MIC ($T > MIC$).

Concentration independent versus concentration dependent

Concentration independent (time dependent) means that the rate and extent of microorganism killing remain unchanged regardless of antimicrobial concentration. The pharmacodynamic parameter that is most often predictive of outcome for concentration independent drugs is $T > MIC$, although the AUC/MIC can be used because the AUC takes both the antimicrobial concentration and time into account. Examples of concentration independent antimicrobials include: beta-lactams, vancomycin, macrolides, aztreonam, carbapenems, clindamycin, tetracyclines, quinupristin/dalfopristin, flucytosine, and azole antifungals.

Concentration dependent (time independent) means that the rate and extent of microorganism killing are a function of the antimicrobial concentration (increase as the concentration increases). The pharmacodynamic parameter that is most often predictive of outcome for concentration dependent drugs is peak/MIC, although the AUC/MIC can be used because the AUC takes both the antimicrobial concentration and time into account. Examples of concentration dependent antimicrobials include: fluoroquinolones, aminoglycosides, and amphotericin B.

Bacteriostatic activity versus bactericidal activity

Bacteriostatic activity refers to the inhibition of bacterial growth, while bactericidal activity refers to killing the bacteria.

Minimum inhibitory concentration (MIC) – The MIC is defined as the lowest concentration of antibiotic that completely inhibits growth of the specific organism being tested.

Minimum bactericidal concentration (MBC) – The MBC is defined as the lowest concentration of antibiotic at which bacteria are killed.

Most of the available evidence supports the preferential use of a bactericidal agent when treating endocarditis, meningitis or osteomyelitis. However, data do not exist to support this practice for other infectious diseases.

Pharmacodynamic properties do not remain constant for all antimicrobials in a class for all microorganisms. In other words, if a drug is concentration dependent and bactericidal against one organism, that does not mean that it, or all the other drugs in its class, are concentration dependent and bactericidal against all organisms. However, because of a lack of data characterizing the pharmacodynamic properties of various antimicrobials against several different organisms, we usually lump antimicrobials into one category.

Vancomycin Dosing

Vancomycin is considered to be a concentration independent or time dependent killer of bacteria. Therefore, increasing antibiotic concentrations beyond the therapeutic threshold will not result in faster killing or eliminate a larger portion of the bacterial population. Vancomycin dosing should be based upon actual body weight (ABW), is generally used at doses of 10-20 mg/kg, and dosing intervals should be renally adjusted. See separate section on Vancomycin Dosing.

“Double coverage”

The use of “double coverage” (two antibiotics used to provide coverage for the same organism) is based upon the following assumptions: the combination provides a broad spectrum of coverage for empiric treatment, before you know the identification and susceptibility of the offending pathogen; the combination may provide additive or synergistic effects against the pathogen; or the combination of antibiotics may decrease or prevent the emergence of resistant bacteria.

Gram-negative Bacteria

Inappropriate initial therapy has been shown to cause increased morbidity and mortality, specifically related to Gram-negative infections (usually *Pseudomonas* and *Acinetobacter* spp.). Thus, double coverage serves the purpose of providing broad spectrum initial empiric coverage until susceptibility data are known. **No evidence exists to support the superiority of combination therapy over monotherapy for Gram negative infections once susceptibilities are known.** Thus, once culture identification and susceptibilities have been reported, de-escalation to a single agent is strongly recommended.

Synergy

- Occurs when inhibitory or bactericidal activity of combination therapy is greater than would be expected from the sum of the activities of the individual agents
- Synergy for Gram-negative infections is of major value only when the bacterium is resistant to one or both of the drugs in the combination.
- Synergy has been best established for beta-lactam and aminoglycoside combinations.
- Synergy between other drug combinations is less predictable and has unclear clinical significance.

Prevention of emergence of resistance

- Emergence of resistance on therapy is uncommon, occurring in 5–10% of infections treated.
- Emergence of resistance to beta-lactams while on therapy with these agents occurs in ~20% of patients infected with organisms with inducible beta-lactamases (*Serratia*,

Enterobacter, Citrobacter, Acinetobacter); beta-lactams are best avoided in these patients if other options are available.

- Emergence of resistance is more common in pneumonia and osteomyelitis due to decreased antibiotic penetration at these sites; attention should be given to appropriate dosing in these patients.
- The addition of additional agents may lead to increased toxicity from adverse drug reactions without preventing emergence of resistance.

Broadening of initial empiric coverage

- Should be considered in patients with life-threatening infections (ventilator-associated pneumonia, sepsis).
- Second agent should offer additional coverage and generally should be an aminoglycoside at UCLA.
- Coverage MUST be narrowed based on culture results; negative cultures can be used to rule out infections with most organisms.

Data regarding combination therapy

- An early study by Hilf suggested that combination therapy was superior to monotherapy in patients with *Pseudomonas* bacteremia BUT 84% of monotherapy patients received inadequate monotherapy with an aminoglycoside. Five more recent studies have not shown a difference in mortality when patients received appropriate monotherapy for *Pseudomonas* bacteremia.
- Recent prospective studies have not shown a benefit to combination therapy over monotherapy in the treatment of serious Gram-negative infections in both non-neutropenic AND neutropenic patients
- Two recent meta-analysis showed no difference in outcomes of patients with sepsis or febrile neutropenia treated with beta-lactams alone vs beta-lactam/aminoglycoside combinations although patients in the latter group had a higher incidence of nephrotoxicity.

Recommendations for use of combination therapy

- Data suggest that monotherapy is sufficient for the treatment of most Gram-negative infections.
- The use of 2 agents to treat proven or suspected Gram-negative infections should be limited to the following situations:
 - **Empiric treatment** of serious infections manifested by hypotension, pressor dependence, or mechanical ventilation (to broaden spectrum) until cultures return
 - **Documented infection** with a resistant Gram-negative organism (particularly *Pseudomonas*, *Acinetobacter*, *Citrobacter*, *Enterobacter*, and *Serratia* when antibiotic penetration to the site of infection is poor (pneumonia, osteomyelitis). Consideration should be given to stopping one of the agents after 5-7 days of therapy when the bacterial burden has decreased.
 - **Documented infection** with a highly-resistant organism only after synergy testing shows an advantage to a beta-lactam/aminoglycoside combination. Infectious Diseases consult strongly advised.
- The second agent should be an aminoglycoside in most cases. Fluoroquinolone resistance is common among Gram-negative organisms at UCLA.
- Double beta-lactam combinations (e.g. zosyn + meropenem) should be avoided.

References:

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Anaerobes

Anaerobic pathogens are normal flora of the oral cavity and the gastrointestinal tract. While oral anaerobic flora are mostly Gram-positive organisms such as *Peptococcus* and *Peptostreptococcus spp.*, the principal anaerobic intestinal flora are Gram-negative bacilli such as *Bacteroides fragilis*, *Prevotella melaninogenica*, and *Fusobacterium spp.* Gram-positive oral anaerobes are widely covered by most of the orally-available agents, including penicillin. However, antibiotic activity against the most common intestinal anaerobic bacteria, *Bacteroides spp.*, is variable.

Anaerobic coverage is indicated in a variety of infectious processes, including but not limited to aspiration pneumonia, intra-abdominal infection, gynecologic infection, and diabetic foot ulcer infection. Antimicrobial agents with appreciable anaerobic activity include the following: Amoxicillin/clavulanate, Ampicillin/sulbactam, Cefotetan, Cefoxitin, Clindamycin, Ertapenem, Imipenem, Meropenem, Metronidazole, Moxifloxacin, Piperacillin/tazobactam, Tigecycline. Double anaerobic coverage is the use of any combination of the above agents, which is prevalent at UCLA. A common combination is piperacillin/tazobactam + metronidazole. Redundant anaerobic coverage is a common problem intervened upon by the Antimicrobial Stewardship Program.

Double anaerobic coverage is not necessary and puts the patient at risk for additional drug toxicities. No data or guidelines support double anaerobic coverage in clinical practice, with two clinical exceptions:

Exceptions:

1. Metronidazole can be added to another agent with anaerobic activity when being used to treat *Clostridium difficile* infection.
2. Clindamycin can be added to another agent with anaerobic activity when being used for the treatment of necrotizing fasciitis.

Laboratory and Clinical Toxicity Monitoring

Medication	Select Toxicities	Minimum Laboratory Monitoring	Clinical Monitoring
Aminoglycosides (gentamicin, tobramycin, amikacin)	Nephrotoxicity, auditory toxicity, vestibular toxicity, neuromuscular blockade	Cr at least 2x/week (for dose-adjustment and nephrotoxicity assessments),	Baseline and periodic hearing and vestibular function (questioning

		serum levels if therapy is to continue >72 hours	audiologic testing with prolonged therapy)
Aztreonam	GI effects, hypersensitivity	Cr weekly (for dose-adjustment assessment)	Hypersensitivity, diarrhea
Carbapenem (meropenem, ertapenem)	Hypersensitivity, GI effects, <i>C. difficile</i> , seizures (especially with high doses or doses not adjusted for renal function)	Cr weekly (for dose-adjustment assessment)	Hypersensitivity, GI effects, seizures (rare)
Cephalosporins	GI effects, hypersensitivity reactions, <i>C. difficile</i>	For IV cephalosporins, Cr weekly except for Ceftriaxone, which does not require dose adjustment for renal function	Hypersensitivity, diarrhea, other GI effects
Ceftriaxone	As above, plus biliary sludging, gallstones	Consider LFTs with prolonged use	As above, plus signs of biliary sludge or gallstones
Clindamycin	Diarrhea, <i>C. difficile</i>	Not routinely indicated	Hypersensitivity, GI effects, photosensitivity
Dalfopristin/quinupristin	Pain or inflammation at infusion site, arthralgia or myalgia, hyperbilirubinemia	LFTs weekly	Phlebitis, arthralgias, myalgias
Daptomycin	GI effects, hypersensitivity, headache, elevated CK, myalgias, rarely rhabdomyolysis	CK weekly, Cr weekly (dose adjustment assessment)	Hypersensitivity, GI effects, myalgias, rhabdomyolysis
Fluoroquinolone (ciprofloxacin, levofloxacin)	GI effects, arthropathy (especially in pediatric patients), tendon rupture, prolongation of QT	Consider periodic Cr and LFTs with prolonged use	Hypersensitivity, GI effects, drug interactions (warfarin), prolongation of QT interval

	interval, CNS effects (esp with ciprofloxacin)		(amiodarone), CNS effects, photosensitivity
Linezolid	Myelosuppression, diarrhea, rash, optic neuritis, peripheral neuropathy	CBC baseline and weekly, consider periodic LFTs with prolonged use	Hypersensitivity, GI effects, neuropathy, drug interactions (serotonergic drugs)
Macrolide (azithromycin, clarithromycin, erythromycin)	GI effects, cholestatic jaundice, QT prolongation, allergic reaction	Consider periodic LFTs with prolonged use; baseline Cr with clarithromycin (dose-adjustment assessment)	Hypersensitivity, GI effects, drug interactions, QT prolongation with risk factors
Metronidazole	Nausea, diarrhea, disulfiram-like reactions with alcohol, metallic taste, reversible neutropenia	Consider baseline LFTs	GI effects. Avoid alcohol
Penicillin class			
Tetracycline class (doxycycline, minocycline)	Photosensitivity, permanent staining of developing teeth (avoid in pregnant women and children <8y), GI effects, rash, vestibular toxicity (minocycline)	Consider periodic LFTs with prolonged use	Hypersensitivity, diarrhea, GI effects, drug interactions, vestibular toxicity (minocycline), photosensitivity (avoid prolonged sun exposure)
Tigecycline	Nausea and vomiting	LFTs weekly	GI effects
TMP/SMX	Nausea, vomiting, hypersensitivity reactions, bone marrow suppression, hyperkalemia	With high dose: consider baseline and periodic measurement of Cr (dose-adjustment and nephrotoxicity assessment), CBC, K, LFTs	Hypersensitivity, GI effects

Vancomycin	Ototoxicity, re man syndrome, nephrotoxicity (usually in combination with other nephrotoxins), phlebitis, reversible neutropenia	Cr baseline and weekly (for potential dose-adjustment and nephrotoxicity assessment), CBC weekly, serum levels as appropriate	Phlebitis, hypersensitivity, GI effects
Antifungal agents			
ABLC	Lower incidence of nephrotoxicity than amphotericin B deoxycholate, infusion-related effects, electrolyte disturbances (hypokalemia, magnesemia)	Twice-weekly Cr, K, Mg; weekly LFTs and CBC	Infusion-related effects
Triazole antifungals (fluconazole, itraconazole, voriconazole, posaconazole)	GI effects, hepatitis, QT prolongation, hypersensitivity	Baseline and periodic LFTs and Cr (dose-adjustment assessment with fluconazole); cyclodextrin vehicle accumulation with IV voriconazole	GI effects, prolongation of QT interval with risk factors, hypersensitivity, photosensitivity, drug-drug interactions
Voriconazole	Transient visual disturbances, cyclodextrin vehicle accumulation with IV formulation in patients with renal dysfunction (clinical significance of risk/benefit unknown)	Serum levels as indicated	As above and visual side effects, hallucinations
Caspofungin	Facial flushing or swelling (histamine mediated but rare), hypersensitivity, hepatitis	LFTs weekly	Hypersensitivity, drug-drug interactions
Antiviral Agents			
Cidofovir	Renal impairment,	Cr (also give saline	GI effects,

	neutropenia, ocular hypotonia, headache, asthenia, alopecia, rash, GI effects	load and probenecid), CBC, UA all 2x/week and before each dose	hypersensitivity (especially with probenecid)
Foscarnet	renal impairment, electrolyte disturbances, seizures, GI effects	Cr 2x/week (dose-adjustment and nephrotoxicity assessments), electrolytes weekly	GI effects, hypersensitivity
Ganciclovir or valganciclovir	Myelosuppression, GI effects	CBC 1-2x/week, Cr weekly (dose-adjustment assessment)	GI effects
Acyclovir or valacyclovir	Malaise, nausea, vomiting, diarrhea, phlebitis (with IV acyclovir), nephrotoxicity and CNS effects with high-dose IV therapy	Cr weekly with IV acyclovir (dose-adjustment and nephrotoxicity assessment)	Phlebitis, CNS effects (IV), GI effects