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.

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), serum levels if therapy is to continue >72 hours	Baseline and periodic hearing and vestibular function (questioning audiologic testing with prolonged therapy)
Aztreonam	GI effects, hypersensitivity	Cr weekly (for dose-adjustment assessment)	Hypersensitivity, diarrhea
Carbapenem (meropenem, ertapenem)	Hypersensitivity, GI effects, *C. difficile*, 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, *C. difficile*	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, *C. difficile*	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 interval, CNS effects (esp with ciprofloxacin)	Consider periodic Cr and LFTs with prolonged use	Hypersensitivity, GI effects, drug interactions (warfarin), prolongation of QT interval (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, neutropenia, ocular hypotonia, headache, asthenia, alopecia, rash, GI effects	Cr (also give saline load and probenecid), CBC, UA all 2x/week and before each dose	GI effects, 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