Introduction to Antimicrobial Therapy

Classification of Antimicrobials

Antimicrobials are drugs that destroy microbes, prevent their multiplication or growth, or prevent their pathogenic action. Antimicrobials differ markedly in their physical, chemical, and pharmacological properties, in antibacterial spectrum of activity, and in mechanisms of action. In general, antimicrobials are classified based on their chemical structure and proposed mechanism of action.

1. Agents that inhibit synthesis of bacterial cell walls.
   - penicillins
   - cephalosporins
   - carbapenems
   - monobactams (aztreonam)
   - vancomycin

2. Agents that affect the function of 30S and 50S ribosomal subunits to cause a reversible inhibition of protein synthesis.
   - chloramphenicol
   - tetracyclines
   - macrolides
   - clindamycin
   - streptogramins (quinupristin/dalfopristin)
   - oxazolidinones (linezolid) – binds to the 23S ribosomal subunit of the 50S ribosome

3. Agents that bind to the 30S ribosomal subunit and alter protein synthesis, eventually leading to cell death.
   - aminoglycosides

4. Agents that affect bacterial nucleic acid metabolism.
   - rifamycins (rifampin) – inhibit RNA polymerase
   - quinolones – inhibit topoisomerase IV and DNA gyrase

5. Agents which block essential enzymes of folate metabolism.
   - trimethoprim
   - sulfonamides

6. Miscellaneous agents
   - daptomycin
   - metronidazole
# How to Choose the Appropriate Antimicrobial

A systematic approach to the selection of antimicrobials

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Antimicrobial therapy is more complicated than matching an antimicrobial drug to a known or suspected pathogen. A number of important factors must be considered in choosing the appropriate antimicrobial agent for a given infection. It often requires a systematic approach which takes into account numerous patient and drug related factors. Optimal and judicious selection of antimicrobial agents for the therapy of infectious diseases requires clinical judgement and detailed knowledge of the pharmacological and microbiological factors.

Antimicrobials are used in three distinct ways: empiric therapy, definitive therapy, and prophylactic or preventative therapy. Empiric therapy, or initial therapy, must cover all the likely pathogens as the infecting organism(s) has not yet been identified. This is often referred to as “broad spectrum” therapy. Once the infecting organism(s) has been identified, therapy becomes definitive, meaning an antimicrobial is chosen that specifically targets the microorganism identified and has the least potential to cause harm to the patient. This changing of antimicrobials
from empiric therapy to definitive therapy often, but not always, results in the use of an
antimicrobial with a narrower, more targeted spectrum of activity. This process is often termed
“narrowing the spectrum” of activity. Finally, therapy may be prophylactic or preventative,
attempting to prevent an infection or its recurrence. The reflex action of many physicians is to
associate fever and prescribe antimicrobials without further evaluation. This is potentially
dangerous and irrational. Antibiotics can cause serious toxicity and injudicious use promotes
selection of resistant bacteria.

Confirm the presence of an Infection

One must confirm the presence of an infection. This is accomplished through a careful
history and physical exam noting all signs and symptoms suggestive of an infection, including
relevant laboratory data. Often, infections may be identified by the following: fever; elevated
white blood cell (WBC) counts; swelling, redness (erythema), purulent drainage from a visible
site; the presence of WBC in normally sterile fluids such as spinal fluid, urine. Symptoms
referable to an organ system must be carefully sought out as they not only help in establishing the
presence of an infection, but also help guide therapy toward potential pathogens. For example, a
patient who complains of flank pain and dysuria may have pyelonephritis (kidney infection) and
therapy would be targeted towards the treatment of gram-negative bacilli such as *E. coli*, as these
pathogens are common causes of urinary tract infections.

Identify the Pathogen

Attempts should be made to microbiologically identify the pathogen. Infected body
materials (e.g. urine, sputum, blood, wound drainage) must be sampled, if at all possible and
practical, before the initiation of antimicrobial therapy. This is important for many reasons, but
most notably a gram stain may be helpful for quick detection of potential organisms causing the
infection (aid in choosing appropriate therapy) and delays in obtaining material until after
antimicrobials have been initiated increase the likelihood of obtaining false negative culture
results. Once gram stain or culture results are obtained the clinician must determine whether the
organism recovered is a true pathogen, a contaminant, or part of the normally expected flora from
the site of collection. Cultures are the most definitive method available for the diagnosis and
eventual treatment of an infection, but they are not always available.

Microbiology laboratories report two important pieces of information relevant to the
practitioner related to antimicrobial therapy, the organism and its susceptibilities to
antimicrobials. Once the organism is identified the susceptibility to various antimicrobials is
reported as susceptible (S), intermediate (I), or resistant (R). This is determined by interpretation of the minimum inhibitory concentration (MIC), which is defined as the lowest concentration of drug that prevents visible bacterial growth after 24 hours of incubation in a specified growth medium. The MIC quantifies the in vitro antibacterial activity of the drug to help predict bacteriologic response to therapy. These MIC values are both organism and antimicrobial specific. It is important to note that interpretation of the MIC requires knowledge of the pharmacokinetics of the drug in humans, the drug’s activity versus the organism, and the site of infection. Susceptible implies that an infection due to the strain may be appropriately treated with the dosage of antimicrobial agent recommended for that type of infection and infecting species (levels of the antimicrobial will probably be equal to or above the MIC). Intermediate implies that a drug may be clinically used in body sites where the drugs are physiologically concentrated or when a high dosage of a drug can be used. This category includes isolates with MICs that approach usually attainable blood and tissue levels and for which response rates may be lower than for susceptible isolates. Resistant implies that strains are not inhibited by the usually achievable systemic concentrations of the agent with normal dosage schedules and/or fall in the range in which specific microbial resistance mechanisms are likely and clinical efficacy has not been reliable (levels of the antimicrobial will most likely not be above the MIC).

There are various susceptibility testing methods.

- **Disk diffusion** – Disk diffusion is the classical method. The antimicrobial agent diffuses from a cellulose filter paper disk (Kirby-Bauer disks) onto a solid medium surface over which bacteria have been streaked. After 24 hours of incubation, inhibition of bacterial growth around the disk, termed the “zone of inhibition”, is measured. This provides only a qualitative result (S, I, R) as no specific MIC number is reported. Based on the size of the zone, the organisms tested can be considered susceptible, intermediate, or resistant.

- **Broth dilution** – Broth dilution utilizes various concentrations of antimicrobial agents in test tubes containing liquid medium to which a standard inoculum of the test organism is
added. The test tubes are incubated for 24 hours and the lowest concentration of antimicrobial agent at which no visible growth is noted is referred to as the MIC.

- **E-test** – E-test (Epsilometer test) is a method by which a gradient of increasing concentrations of the test antimicrobial is incorporated into a single plastic coated strip. The strip is placed on solid agar onto which the test organism has been streaked. After overnight incubation, the MIC is determined by visually identifying the intersection of the lowest point of the elliptical zone of growth inhibition and the gradient strip.

The above mentioned information related to the in-vitro activity of the antimicrobials is critical, but is only a guide as to whether or not an antimicrobial will be effective in an infection. Successful therapy also depends upon achieving a drug concentration that is sufficient to inhibit or kill the bacteria at the site of infection without harming the patient. Accordingly, one must also consider the following pharmacologic drug and host factors.
Drugs Factors

Pharmacokinetics

The pharmacokinetic disposition of an agent is an important consideration when choosing antimicrobial therapy. Pharmacokinetics encompasses all the ways that the body manipulates a drug. This includes absorption, distribution, metabolism, and excretion.

Absorption of a drug occurs anywhere that it is administered, except when it is administered directly into a physiologic fluid compartment (e.g. blood, cerebrospinal fluid). This includes intramuscular, subcutaneous, or topical administration as well as absorption from the gastrointestinal tract after oral, rectal, or tube administration. The amount of drug that reaches the systemic circulation is expressed as a percentage of the total amount that could have been absorbed. This percentage is defined as the drug’s bioavailability. It may also be reported as absolute bioavailability, determined by direct comparison of an intravenous form of the drug with the absorbed form. By definition, most intravenous forms of a drug are 100% bioavailable because all of the administered dose enters the bloodstream. Factors which may affect absorption and bioavailability include drug interactions with other compounds or food that may bind the drug and prevent it from being absorbed or a disease state that may adversely affect the site of absorption (i.e. diarrhea, bowel obstruction).

Distribution is most commonly described by the volume of distribution. This represents a value that relates drug concentration in the system to the amount of drug present in that system. Many factors influence the volume of distribution including lipid solubility, blood flow to tissues, pH, and protein binding. Drugs with small distribution volumes have limited distribution, whereas drugs with large distribution volumes are extensively distributed throughout the body.
Drugs and other compounds are metabolized by a variety of reactions. Most commonly, metabolism occurs in the liver, but other organs have the ability to metabolize drugs. Drug metabolism is classified as either a Phase I or Phase II reaction. Phase I reactions cause inactivation of the substrate, with the resulting compound being more polar than the parent compound. This facilitates elimination from the body. Phase I reactions generally are under the control of the cytochrome P-450 (CYP) system. CYP enzymes are affected by a number of factors that stimulate or inhibit their ability to metabolize drugs. Phase II reactions involve conjugation of the parent compound with larger molecules, which increases the polarity of the parent, again facilitating excretion.

Elimination of a drug from the body occurs by two mechanisms, renal and nonrenal clearance. Renal clearance describes the rate at which the body eliminates a substance via the kidneys. Nonrenal clearance primarily denotes hepatic clearance, but it may not be the only route of nonrenal clearance. Rather, nonrenal clearance is a generic term that describes the sum of clearance pathways that do not involve the kidneys and may include the biliary tree or the intestine. Clearance also affects the half-life (t\(_{1/2}\)). The half-life of a drug is the amount of time required for the blood concentration of the drug to decrease by half. The steady-state concentration (amount of drug administered equals the amount of drug excreted) has been achieved once the patient has been taking the drug for about 4-5 half-lives. Half-lives vary from patient to patient according to end organ function and protein binding.

Relationship Between Antimicrobial Pharmacokinetics and the Minimum Inhibitory Concentration

**Pharmacodynamics**

Pharmacodynamics aims at understanding the relationships between drug concentrations and effects, both desirable (e.g. bacterial killing) and undesirable (e.g. side effects). Desirable effects can be classified as either static (inhibitory) or cidal (lethal). Depending on the
mechanism of action, an antimicrobial agent may inhibit growth or replication or cause bacterial cell death. Interference in the development of a bacterial cell wall or membrane (e.g. beta-lactams, vancomycin) results in cell lysis and death. Antimicrobials that inhibit nucleic acid synthesis (e.g. quinolones) or protein synthesis (e.g. aminoglycosides) also lead ultimately to cell death. In contrast, inhibition of folic acid synthesis (e.g. sulfonamides) may only cause inhibition of bacterial growth. Another factor that affects whether a drug is bacteriostatic or bactericidal is the antimicrobial concentration at the site of infection. Antimicrobials may be static at low concentrations, but cidal at higher concentrations. If the host is compromised or infection is severe and/or invasive, then cidal therapy is preferred.

Concentration dependent killing agents (e.g. quinolones, aminoglycosides) eliminate bacteria when their concentrations are well above the MIC of the organism. When the ratio of the concentration at the site of infection to the MIC is increased further, greater killing occurs. The ratio of the C\text{max} (peak) of the antimicrobial divided by the MIC of the organism is the clinical correlate used as the pharmacodynamic predictor for outcome for concentration dependent killing agents (peak/MIC ratio = important). Concentration-independent (time-dependent) killing agents (e.g. penicillins, cephalosporins) kill bacteria only when the concentration at the site of the bacteria is higher than the MIC of the organism. Once the concentration at the bacterial site is more than four times higher than the MIC, little additional killing occurs (see figure below). The time during which the serum drug concentration is greater than the MIC is the pharmacodynamic parameter that appears to predict efficacy for these agents (time>MIC = important).

Concentration-dependent [Tobramycin (aminoglycoside), Ciprofloxacin (quinolone)] and Time-dependent [Ticarcillin (penicillin)] agents versus *Pseudomonas aeruginosa*
The post antibiotic effect (PAE) is the delayed regrowth of bacteria following exposure to an antimicrobial (i.e. continued suppression of normal growth in the absence of antibiotic levels above the MIC of the organism). The presence and duration of PAE varies according to drug-bug combination. Most beta-lactam agents (e.g. penicillins, cephalosporins) exhibit a PAE of about 1-2 hours against gram-positive organisms. Against gram-negative organisms, however, most beta-lactams exhibit a negligible PAE while aminoglycosides and quinolones have PAE ≥ 2 hours. The clinical significance of the PAE is unknown, but it helps choose the appropriate dosing interval for the antimicrobial.

It is important for practitioners to avoid toxic drugs whenever possible. Antibiotics may be associated with central nervous system toxicity when not adjusted appropriately for renal dysfunction. Prolonged use of various agents may predispose patients to hematologic toxicities. Similarly, the nephrotoxicity potential of aminoglycosides and vancomycin may worsen preexisting renal dysfunction or augment the risk of other non-antimicrobial nephrotoxic drugs.

The costs of drug therapy are increasing dramatically. Greater attention is being paid to the pharmacoeconomics of drug therapy where patient outcomes are valued and the costs associated with those outcomes estimated. The total cost of antimicrobial therapy, however, includes much more than just acquisition cost of drugs. These include factors such as storage, preparation, distribution, and administration, as well as all the costs incurred from monitoring for adverse effects and factors such as length of hospitalization, readmissions, and all directly provided health care goods and services. More difficult to measure, but important, are the indirect costs such as patient quality of life issues. Many new oral antimicrobials have been approved that can be used in place of more expensive intravenous therapy. In addition, many older, less expensive agents may also be appropriate choices. Factors to weigh include safety, effectiveness, tolerability, patient adherence, and potential drug-drug interactions. In some instances, more expensive agents may be warranted to avoid adverse outcomes.

**Host Factors**

*Allergy*

The allergy history is important when prescribing any drug. Adverse drug reactions occur in up to 30% of hospitalized patients with allergic drug reactions accounting for 5-20% of all observed adverse drug reactions. Accordingly, allergic drug reactions can be severe and life threatening. A previous history of allergic reaction to a drug being considered or one that is immunochemically similar is the most reliable risk factor for development of a subsequent allergic reaction. The most common example is the patient who presents with a history of
penicillin allergy, in whom all structurally related penicillin compounds should be avoided, and in whom the possibility of a reaction should be considered with the use of other beta-lactam antibiotics. It is important to obtain an adequate and complete history of patient drug allergies to determine whether the reaction was intolerance, toxicity, or true allergy. Many patients confuse common adverse drug effects as allergies (e.g. gastrointestinal intolerance from erythromycin is common, but is not considered an allergic reaction and thus, erythromycin could be used if necessary in this patient). Avoid the use of a drug (or related compound) if a patient has previously experienced a true allergic reaction (anaphylaxis, bronchospasm, etc.). Patients with delayed reactions to penicillin (skin rash) can generally receive cephalosporins (5-10% cross reactivity). Patients with type I hypersensitivity reactions to penicillins (anaphylaxis) should not receive cephalosporins (consider alternatives: e.g. aztreonam, quinolones, sulfa drugs, vancomycin).

Age

The likelihood of isolating a particular bacteria as a cause of an infection may be dependent on the patient’s age. For example, with bacterial meningitis neonates are at a greater risk of meningitis caused by Listeria sp. and group B Streptococcus sp., adults are at a greater risk of meningitis caused by Streptococcus pneumoniae and Neisseria meningitidis, and elderly patients are at a greater risk of meningitis caused by Streptococcus pneumoniae and Listeria sp.

Renal and hepatic function also varies with age and may affect a patient’s ability to eliminate a drug. In premature and newborn children and the elderly, renal function is diminished and half-lives of drugs excreted by the kidneys may be increased (patients require less drug). Similarly, hepatic function is diminished in neonates.

Pregnancy

During pregnancy, the fetus is at risk for drug teratogenicity and the pharmacokinetic disposition of certain drugs may be altered. All antimicrobials cross the placenta in varying degrees so one should avoid agents known to be teratogenic. Penicillins, cephalosporins, and erythromycin appear safe in pregnancy, while it would be prudent to avoid ticarcillin, metronidazole (teratogenic in rodents), and tetracyclines (bind to developing bone and teeth → discoloration). The teratogenicity of some other agents remains unknown (e.g. quinolones, rifampin, trimethoprim). Penicillins, cephalosporins, and aminoglycosides are cleared more rapidly during pregnancy (increases in intravascular volume, glomerular filtration rate and hepatic
and metabolic activities) and increased dosages may be necessary to achieve therapeutic levels during late pregnancy.

**Genetic or metabolic abnormalities**

Inherited or acquired metabolic abnormalities may influence antimicrobial therapy. Patients with peripheral vascular disease may have impaired absorption of intramuscularly administered drugs. Patients with severe glucose-6-phosphate dehydrogenase (G6PD) deficiency may develop hemolysis when administered sulfonamides, nitrofurantoin, dapsone, antimalarials, and chloramphenicol. Although mild deficiencies are found in African-Americans, the more severe forms of the disease are generally found in persons of Eastern Mediterranean origin.

**Renal or hepatic function**

Patients with diminished renal or hepatic function, or both, will accumulate certain drugs metabolized and/or excreted by these routes. These patients are at an increased risk of drug toxicity unless the dosage is adjusted. It is important to remember that renal excretion is the most important route of elimination for the majority of antimicrobials. The presence of severe liver disease may also require dosage adjustment for agents relying predominantly on hepatic metabolism for elimination (e.g. clindamycin, macrolides, metronidazole, and rifampin).

**Site of infection**

Of all the host factors to be considered in the choice of an antimicrobial agent, none is more important than the site of infection. Identification of the site of infection or the likely source of a bacteremia defines the most likely organisms. This is especially helpful when choosing an agent for empiric therapy. For example, the majority of urinary tract infections are caused by gram-negative bacilli, like *E. coli*, whereas bacteremia from an intravascular catheter is often caused by *Staphylococcus* sp. In addition, the site of infection determines not only the choice of agent, but the dose and route by which it should be administered. For antimicrobial therapy to be effective, an adequate concentration of the drug must be delivered to the site of infection. Serum concentrations of antimicrobial agents are relatively easy to determine and therefore are often used as a guide in the therapy, but except in the cases of bacteremias, antimicrobial efficacy is more likely determined by the tissue concentration at the site of infection. The minimal drug concentration at the infected site should be approximately equal to the MIC for the infecting organism, although in most instances it is recommended to achieve multiples of this concentration if possible (especially concentration dependent killing agents).
Access of antimicrobials to sites of infection depends on multiple factors. If the infection is in the cerebrospinal fluid, the drug must cross the blood-brain barrier and many antimicrobials do so poorly. Penetration of drugs into infected sites always depends on passive diffusion and this penetration is proportional to the concentration of free drug in the plasma or extracellular fluid. Therefore, drugs that are extensively protein bound may not penetrate to the same extent as those that are bound to a lesser extent. Because of the problems associated with antimicrobial penetration, the treatment of infections such as meningitis, endocarditis, and osteomyelitis often require higher doses and more prolonged therapy with agents that have adequate penetration to the site of infection. With regards to the route of administration, while oral administration is preferred whenever possible, intravenous administration of antimicrobials is usually recommended in seriously ill patients in whom predictable concentrations of drug must be achieved (e.g. bacteremia, meningitis, endocarditis).

Concomitant drug therapy

Concomitant drug therapy influences the selection of appropriate drug therapy, the dosage, and necessary monitoring. Drug interactions may increase (increased risk of toxicity) or decrease (potential for lack of efficacy) concentrations of the antimicrobial or the antimicrobials may increase or decrease concentrations of other drugs in a patient’s regimen. Pharmacokinetic drug interactions alter the absorption, transport, distribution, metabolism, or excretion of a drug (corresponding changes in therapeutic effect may or may not occur). For example, 1) decreased absorption of quinolones is caused by concomitant administration with multivalent cations (calcium, magnesium, aluminum containing antacids), and 2) rifampin decreases the anticoagulant effect of warfarin secondary to increased hepatic metabolism caused by rifampin. Pharmacodynamic drug interactions alter the pharmacologic response of a drug. The simultaneous use of two or more antimicrobials has a certain rationale and is recommended in specific situations. Selection of the appropriate combination, however, requires an understanding of the potential for an interaction between antimicrobial agents. Interactions may affect the organism or the patient. When discussing antimicrobial activity, combinations of antimicrobials may be synergistic, antagonistic, or indifferent. Synergy results when the addition of drug A to drug B results in a total antimicrobial activity greater than the expected sum of the two agents (e.g. penicillin + aminoglycoside against Enterococci). Antagonism occurs when the addition of drug A to drug B results in a combined activity less than the sum of drug A + drug B. Indifference means that the addition of drug A to drug B results in activity equal to the anticipated sum activity of drug A + drug B (see figure below). Combinations of drugs may also
have additive or superadditive toxicity such that agents with overlapping toxicity profiles may increase the risk of adverse effects. For example, vancomycin used alone usually has minimal renal toxicity, but when vancomycin is given with an aminoglycoside, the renal toxicity risk of the aminoglycoside is increased.

**Underlying disease states**

Certain disease states will predispose patients to a particular infectious disease or alter the most likely organisms causing an infection. Immunosuppressive diseases (malignancies, organ transplant patients, HIV+ patients) predispose patients to infections. In addition, the type of organisms causing the infections may be different than expected in a normal host. For example, bacterial meningitis in an otherwise healthy adult is commonly caused by *Streptococcus pneumoniae* or *Neisseria meningitidis*, but may also be caused by *Listeria monocytogenes* in a patient with lymphoma.

As mentioned previously, renal and hepatic function when compromised affects the elimination of antimicrobials from the body. There is an increased risk of toxicity if antimicrobial doses are not adjusted for end-organ function.

**Monitoring the response**

Although several laboratory tests are available to assist in the monitoring of antimicrobial therapy, clinical assessment remains the most important method for determining the efficacy of treatment. Culture and sensitivity reports from specimens sent to the microbiology laboratory must be reviewed, and the therapy changed accordingly. Use of agents with the narrowest spectrum of activity against identified pathogens is recommended.

Patient monitoring should include many of the same parameters used to diagnose the infection. The WBC count and temperature should start to normalize. Physical complaints from
the patient should also diminish (i.e. decreased pain, decreased cough). Radiologic improvement may lag behind clinical improvement. Determination of serum (or other fluid) levels of antimicrobials may be useful in assuring outcome, preventing toxicity, or both. There are only a few antimicrobials that require serum concentration monitoring, and then only in selected situations (i.e. aminoglycosides). It is also important to monitor patient tolerability of the antimicrobial regimen. Appropriate laboratory tests (e.g. serum creatinine, liver enzymes) should be monitored to minimize or avoid antimicrobial drug toxicity. The antibiotic route of administration should be evaluated daily and streamlining from intravenous to oral antimicrobials should be attempted as signs of infection improve for patients with functioning gastrointestinal tracts (general exceptions are bloodstream and central nervous system infections).

Patients not responding to an appropriate treatment in about 2 to 3 days should be reevaluated to ensure that infection is the correct diagnosis, therapeutic drug concentrations are being achieved, the patient is not immunosuppressed, the patient does not have an isolated infection (abscess, foreign body), or resistance has not developed.

**Conclusion**

Optimal use of antimicrobial agents requires consideration of a number of important factors that may influence the choice of an appropriate agent and that determine the most effective dose and route of administration. The goal of therapy is always to maximize efficacy while limiting patient harm. Rational clinical judgement and appropriate disease and drug therapy monitoring remain the most important determinants of a successful outcome.