Rational Antimicrobial Selection & antimicrobial Prophylaxis

Rational Antimicrobial Selection

- **The initial selection of antimicrobial therapy may be empirical, prior to documentation and identification of the offending organism.**

- **A delay in antimicrobial therapy for infections may sometimes result in serious morbidity and mortality.**

Rational Antimicrobial Selection

- **Empirical antimicrobial therapy** selection should be based on:

1. The patient's history and physical examination.

2. Results of Gram stains or other rapidly performed tests on specimens from the infected site.

3. Knowledge of the most likely offending organism for the infection in question.

4. Institution's local susceptibility patterns.

Rational Antimicrobial Selection

Identification of the pathogen:

- **Identification of the pathogen** and **antimicrobial susceptibility** of the pathogen are the **most important factors in determining the choice of antimicrobial therapy.**

- **Infected materials must be sampled with starting of any antimicrobial therapy for two reasons:**

a) **A Gram stain might reveal bacteria, or an acid-fast stain might detect mycobacteria or actinomycetes.**

b) **The premature use of antimicrobials can suppress the growth of pathogens which might result in false-negative cultures results.**

Rational Antimicrobial Selection

- **Blood cultures** should be performed in the acutely ill febrile patient.

- **Infected materials** (blood, sputum, urine, stool, abscesses, wound or sinus drainage, spinal fluid, and joint fluid, ...), from the suspected infection site must be obtained and tested.

- **When a pathogenic microorganism is identified, antimicrobial susceptibility testing should be performed.**

Rational Antimicrobial Selection

- **When the pathogen has been identified, specific definitive antimicrobial therapy should be promptly administered.**

Selection of presumptive therapy:

A variety of factors must be considered:

1) **The severity and acuity of the disease.**
2) **Local epidemiology and antibiogram.**
3) **Patient's history and host factors.**
4) **Factors related to the drugs to be used.**
5) **The necessity for using multiple agents.**

Rational Antimicrobial Selection

- **In addition, there are generally accepted drugs of first choice for the treatment of most pathogens.**

- **Drugs of choice are compiled from a variety of sources and are intended as guidelines rather than as specific rules for antimicrobial use.**

Antibiograms (antibiotic susceptibilities):

- **Local antimicrobial susceptibility data, not that from other institutions or national compilations.**

- **Susceptibility of bacteria can differ substantially among hospitals within a community.**

Rational Antimicrobial Selection

Patient History:

- **As part of the medical history, the place where the infection was acquired should be determined, home (community acquired), nursing home environment, or hospital (nosocomial).**

- **Nursing home patients can be exposed to potentially more resistant organisms because they are often surrounded by ill patients who are receiving antibiotics.**

Rational Antimicrobial Selection

Host Factors:

Allergy:

- Allergy to an antimicrobial agent generally precludes its use.

- Cephalosporins should be avoided in patients allergic to penicillin for immediate or accelerated reactions (anaphylaxis, laryngospasm), but can be given under close supervision in patients with skin rash.

Rational Antimicrobial Selection

Age:

- **Age is an important for identification of the likely etiologic agent and in the ability to eliminate the drug.**

- **In bacterial meningitis, the pathogens differ as the patient grows from the neonatal period through infancy and childhood into adulthood.**

- **For neonates, hepatic and liver functions are not well developed.**

Rational Antimicrobial Selection

- **Neonates (especially when premature) can develop kernicterus when given sulfonamides, because of displacement of bilirubin from serum albumin.**

- **The major change in the elderly is decreased renal function, leading to increased adverse effects of antimicrobials eliminated by the kidney (aminoglycosides).**

Rational Antimicrobial Selection

Pregnancy:

- During pregnancy, the fetus is at risk for drug teratogenicity.

- The disposition of certain drugs by the mother may be altered.

- Penicillins, cephalosporins, and aminoglycosides are cleared more rapidly during pregnancy, because of increases in intravascular volume, glomerular filtration rate, and hepatic metabolic activities.

Rational Antimicrobial Selection

- This results in a maternal serum antimicrobial concentrations 50% lower than in the nonpregnant state.

- Thus, increased dosages of certain compounds might be necessary to achieve therapeutic levels during late pregnancy.

Rational Antimicrobial Selection

Metabolic or Genetic Variation:

- **Inherited or acquired metabolic abnormalities will influence the therapy of infectious diseases in a variety of ways.**

- **Patients with impaired peripheral vascular flow may not absorb drugs given by intramuscular injection.**

- **Patients who are slow acetylators of isoniazid are at greater risk for peripheral neuropathy.**

Rational Antimicrobial Selection

- **Patients with severe deficiency of glucose-6-phosphate dehydrogenase can develop significant hemolysis when exposed to dapsone, sulfonamides, nitrofurantoin, nalidixic acid, and antimalarials.**

- **The antiretroviral drug abacavir is associated with severe hypersensitivity reaction (fever, rash, abdominal pain, and respiratory distress) in the presence of a human leukocyte antigen allele HLA-B*5701.**

Rational Antimicrobial Selection

Organ Dysfunction:

- Patients with diminished renal or hepatic function or both will accumulate certain drugs unless the dosage is adjusted.

- Antibiotics that should be adjusted in severe liver disease include clindamycin, erythromycin, metronidazole, and rifampin.

- Significant accumulation can occur when both liver dysfunction and renal dysfunction are present for the following drugs: cefotaxime, nafcillin, piperacillin, and sulfamethoxazole.

Rational Antimicrobial Selection

Concomitant Drugs:

- May influence the drug selection, dose, and monitoring.

- Administration of isoniazid to a patient who is also receiving phenytoin can result in phenytoin toxicity secondary to inhibition of phenytoin metabolism by isoniazid.

- Drugs that possess similar adverse effect profiles can produce enhanced adverse effects (two drugs that cause nephrotoxicity or neutropenia).

Rational Antimicrobial Selection

Major Drug Interactions with Antimicrobials:

1. Amino glycosides with:

A. Neuromuscular blocking agents: additive NML block.

B. Nephro- and Oto-toxins (Amphotericin, cisplatin, cyclosporine [N], furosemide [O], NSAIDs [N], radiocontrast media [N], vancomycin [N]). additive effects.

Rational Antimicrobial Selection

2. Amphotericin B with nephrotoxins (aminoglycosides, cidofovir, cyclosporine, foscarnet, pentamidine): additive adverse effects.

3. Chloramphenicol with (phenytoin, tolbutamide, ethanol): decreased metabolism of other agents.

4. Foscarnet with pentamidine IV: increased risk of severe nephrotoxicity/hypocalcemia.

5. Isoniazid with carbamazepine, phenytoin: Decreased metabolism of other agents (nausea, vomiting, nystagmus, ataxia).

Rational Antimicrobial Selection

6. Macrolides/azalides with

A. Digoxin: increased digoxin bioavailability.

B. Theophylline: decreased metabolism of theophylline.

7. Metronidazole with ethanol (drugs containing ethanol): disulfiram-like reaction.

8. Penicillins and cephalosporins with probenecid, aspirin: Blocked excretion of β-lactams.

Rational Antimicrobial Selection

9. Ciprofloxacin/norfloxacin with theophylline: decreased metabolism of theophylline.

10. Quinolones with:

A. Classes Ia and III antiarrhythmics: increased Q-T interval.

B. Multivalent cations (antacids, iron, sucralfate, zinc, vitamins, dairy, citric acid), didanosine: decreased absorption of quinolone.

Rational Antimicrobial Selection

11. **Rifampin with azoles, cyclosporine, methadone propranolol, PIs, oral contraceptives, tacrolimus, warfarin: increased metabolism of other agents.**

12. **Sulfonamides with sulfonylureas, phenytoin, warfarin: displacement from binding to albumin.**

13. **Tetracyclines with:**

A. **Antacids, iron, calcium, sucralfate: decreased absorption of tetracycline.**

B. **Digoxin: increased digoxin bioavailability.**

Rational Antimicrobial Selection

Drug Factors:

PK and PD Considerations:

- **Important parameters to be considered are the minimal inhibitory concentration (MIC) and the time the concentration is above MIC.**

- **Aminoglycosides exhibit concentration-dependent bactericidal effects, which allows a once-daily aminoglycosides administration.**

- **These drugs are given as a single large daily dose to maximize the peak:MIC ratio.**

Rational Antimicrobial Selection

- **They also possess a postantibiotic effect (persistent suppression of organism growth after concentrations decrease below the MIC) that appears to contribute to the success of high-dose, once-daily administration.**

- **Fluoroquinolones exhibit concentration-dependent killing activity, but optimal killing appears to be characterized by the AUC:MIC ratio.**

Rational Antimicrobial Selection

- **β-Lactams display time-dependent bactericidal effects.**

- **Therefore, the important pharmacodynamic relationship for these antimicrobials is the duration that drug concentrations exceed the MIC.**

- **Frequent small doses, continuous infusion, or prolonged infusion of β-lactams appears to be correlated with positive outcomes.**

Rational Antimicrobial Selection

Tissue Penetration:

- **One important factors in treating an infection is the presence of the antimicrobial agent in an active form and at adequate concentration at the site of injection.**

- **Drugs that have low biliary fluid concentrations are not useful in the treatment of cholecystitis and cholangitis.**

- **Some drugs have poor penetration to deep infections, such as abscesses, where various factors such as acid pH, WBC products, and various enzymes can inactivate even high concentrations of certain drugs.**

Rational Antimicrobial Selection

- **Drugs that do not reach significant concentrations in the CSF should be avoided in treatment of bacterial meningitis.**

- **Body fluids where drug concentration data are clinically relevant include CSF, urine, synovial fluid, and peritoneal fluid.**

- **Parenteral therapy is indicated in febrile neutropenia, meningitis, endocarditis, and osteomyelitis.**

Rational Antimicrobial Selection

- **Severe pneumonia often is treated initially with IV antibiotics and switched to oral therapy as clinical improvement is evident.**

- **Patients treated in the ambulatory setting for upper respiratory tract infections (pharyngitis, bronchitis, sinusitis, and otitis media), lower respiratory tract infections, skin and soft-tissue infections, uncomplicated urinary tract infections, and selected sexually transmitted diseases can usually receive oral therapy.**

Rational Antimicrobial Selection

Drug Toxicity:

- It is necessary to avoid toxic drugs whenever possible.

- Antibiotics associated with CNS toxicities, when not dose-adjusted for renal function, include penicillins, cephalosporins, quinolones, and imipenem.

- Hematologic toxicities occur with prolonged use of nafcillin (neutropenia), piperacillin (platelet dysfunction), cefotetan (hypoprothrombinemia), chloramphenicol (bone marrow suppression, both idiosyncratic and dose-related toxicity), and trimethoprim (megaloblastic anemia).

Rational Antimicrobial Selection

- **Reversible nephrotoxicity classically is associated with aminoglycosides and vancomycin.**
- **Irreversible ototoxicity can occur with aminoglycosides.**
- **In the outpatient setting, patients must be counseled regarding photosensitivity with azithromycin, quinolones, tetracyclines, pyrazinamide, sulfamethoxazole, and trimethoprim.**
- **Many antibiotics have been implicated in causing diarrhea and colitis secondary to *Clostridium difficile* superinfection.**

Rational Antimicrobial Selection

Penicillins & Cephalosporins:

- **Hypersensitivity reactions and rash, drug fever, diarrhea, emesis, abdominal pain, hepatitis, interstitial nephritis, leukopenia, thrombocytopenia, Coomb's positive-hemolytic anemia, *C. difficile* colitis, electrolyte abnormalities, seizures.**

Rational Antimicrobial Selection

Carbapenems:

- **Hypersensitivity reactions and rash, headache, nausea, diarrhea, seizures, drug fever, eosinophilia, thrombocytopenia, hepatitis, *C. difficile* colitis.**

Monobactams:

- **Rash, diarrhea, nausea, hepatitis, thrombocytopenia, *C. difficile* colitis.**

Rational Antimicrobial Selection

Aminoglycosides:

- **Tubular necrosis and renal failure, vestibular and cochlear toxicity, neuromuscular blockade, vertigo, anemia, hypersensitivity.**

Glycopeptides:

- **Red man syndrome, phlebitis, renal dysfunction, neutropenia, leukopenia, eosinophilia, thrombocytopenia, drug fever.**

Rational Antimicrobial Selection

Lipopeptides (daptomycin):

- **Hepatotoxicity, CPK elevation with or without myopathy, diarrhea, eosinophilic pneumonia, *C. difficile* colitis.**

Oxazolidinones (linezolid):

- **Myelosuppression (thrombocytopenia, leukopenia, and anemia), peripheral neuropathy, optic neuropathy, blindness, lactic acidosis, diarrhea, nausea, serotonin syndrome, interstitial nephritis.**

Rational Antimicrobial Selection

Tetracyclines:

- **GI upset, nausea, vomiting, diarrhea, hepatotoxicity, esophageal ulcerations, photosensitivity, azotemia, visual disturbances, vertigo, hyperpigmentation, deposition on teeth, hemolytic anemia, pseudotumor cerebri, pancreatitis, *C. difficile* colitis.**

Chloramphenicol:

- **Myelosuppression, aplastic anemia, "gray baby syndrome," optic neuritis, peripheral neuropathy, digital paresthesias, GI upset, *C. difficile* colitis, hypersensitivity.**

Rational Antimicrobial Selection

Rifamycines:

- **Discoloration of urine, tears, contact lens, sweat, hepatotoxicity, GI upset, flu-like syndrome, hypersensitivity, thrombocytopenia, leukopenia, drug fever, interstitial nephritis, thrombocytopenia.**

Macrolides/azalide:

- **GI intolerance, diarrhea, prolonged QTc, cholestatic hepatitis, reversible ototoxicity, *torsade de pointes*, rash, hypothermia, exacerbation of myasthenia gravis.**

Rational Antimicrobial Selection

Clindamycin:

- **Diarrhea, *C. difficile* colitis, nausea, vomiting, generalized rash, hypersensitivity.**

Fluoroquinolones:

- **GI intolerance, headache, malaise, insomnia, dizziness, photosensitivity, QTc prolongation, tendon rupture, peripheral neuropathy, crystalluria, seizure, interstitial nephritis, Stevens-Johnson syndrome, allergic pneumonitis, *C. difficile* colitis.**

Rational Antimicrobial Selection

Sulfonamides and trimethoprim:

- GI intolerance, rash, hyperkalemia, bone marrow suppression (anemia with folate deficiency, thrombocytopenia, and leukopenia), serum sickness, hepatitis, photosensitivity, crystalluria with azotemia, urolithiasis, methemoglobinemia, Stevens-Johnson syndrome, toxic epidermal necrolysis, aseptic meningitis, pancreatitis, interstitial nephritis, neurologic toxicity.

Rational Antimicrobial Selection

Metronidazole:

- GI intolerance, headache, metallic taste, dark urine, peripheral neuropathy, disulfiram reactions with alcohol, insomnia, stomatitis, aseptic meningitis, dysarthria.

Polymyxins (polymyxin B & colistin):

- Nephrotoxicity, neurotoxicity (paresthesia, vertigo, ataxia, blurred vision, slurred speech), neuromuscular blockade, bronchospasm (administered via inhalation).

Rational Antimicrobial Selection

Failure of antimicrobial therapy:

- **Patients who fail to respond over 2 to 3 days require a thorough reevaluation.**

Causes of failure:

a) **The disease is not infectious or is nonbacterial in origin.**

b) **There is an undetected pathogen in a polymicrobial infection.**

c) **Factors directly related to drug selection, the host, or the pathogen.**

d) **Laboratory error in identification, susceptibility testing, or both.**

Rational Antimicrobial Selection

Failures Caused by Drug Selection:

1) Inappropriate selection of drug , dosage, or route of administration.

2) Reduced absorption of a drug, resulting in subtherapeutic concentrations, because of:

a. GI disease (short-bowel syndrome).

b. Drug interaction (complexation of fluoroquinolones with multivalent cations).

3) Accelerated drug elimination (cystic fibrosis or during pregnancy), resulting in low concentrations.

Rational Antimicrobial Selection

4) Poor penetration into the site of infection (for sites such as the CNS, eye, and prostate gland).

5) Chemical inactivation of the drug at the site of infection.

Rational Antimicrobial Selection

Failures Caused by Host Factors:

- Patients who are immunosuppressed (granulocytopenia from chemotherapy or AIDS) may respond poorly to therapy because their defenses are inadequate to eradicate the infection despite seemingly adequate drug regimens.

- The need for surgical drainage of abscesses or removal of foreign bodies, necrotic tissue, or both. These infections will not be effectively treated without surgical procedures.

Rational Antimicrobial Selection

Failures Caused by Microorganisms (Resistance):

- **Intrinsic resistance: is when the antimicrobial agent never had activity against the bacterial species. (Gram-negative bacteria are naturally resistant to vancomycin because the drug cannot penetrate the outer membrane of Gram negative bacteria).**

- **Acquired resistance: is when the antimicrobial agent was originally active against the bacterial species but the genetic makeup of the bacteria has changed so the drug can no longer be effective.**

Rational Antimicrobial Selection

- **Bacteria develop acquired resistance by any of the following mechanisms:**

a. Alteration in the target site.

b. Change in membrane permeability.

c. Expression of an efflux pump.

d. Drug inactivation through either β-lactamases or aminoglycoside-modifying enzymes is the predominant mechanism of resistance. The expression of β-lactamases can be induced or constitutive.

Rational Antimicrobial Selection

- **The increase in resistance among bacteria is believed to be a result of:**

1. **Continued overuse of antimicrobials in the community and in hospitals.**

2. **Increasing prevalence of immunosuppressed patients receiving long-term suppressive antimicrobials for the prevention of infections.**

Rational Antimicrobial Selection

- **Enterococci have been isolated with multiple resistance patterns.**

- **They may be resistant to:**

1. **β-lactams (β-lactamase production, altered penicillin-binding proteins [PBPs], or both)**

2. **Vancomycin (alterations in peptidoglycan synthesis).**

3. **High levels of aminoglycosides degradating enzymes.**

Rational Antimicrobial Selection

- **Pneumococci resistant to penicillins, certain cephalosporins, and macrolides are increasingly common. These organisms generally are susceptible to vancomycin, the new fluoroquinolones (moxifloxacin and trovafloxacin), and cefotaxime or ceftriaxone.**

- **Antimicrobial agents such as linezolid, daptomycin, telavancin (semi-synthetic derivative of vancomycin), and tigecycline (new tetracycline) have been targeted at resistant Gram-positive bacteria.**

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Rational Antimicrobial Selection

- **Treatment of an infection caused by *Enterobacter*, *Citrobacter*, *Serratia*, or P*. aeruginosa* with a third-generation cephalosporin or aztreonam may produce an initial clinical response by eradicating all the susceptible bacteria in the population.**

- **Within a few days, however, the highly resistant subpopulations have a selective advantage and can overgrow at the infection site to produce a relapse.**

- **These bacteria usually retain susceptibility to aminoglycosides, carbapenems, and fluoroquinolones but are resistant to all other β-lactams.**

Rational Antimicrobial Selection

- **Host defenses are extremely important in this scenario.**

- **Debilitated patients with pulmonary infections, abscesses, or osteomyelitis are at high risk for drug failure.**

- **In these situations, a combination regimen to prevent the emergence of resistance or the use of carbapenem or a fluoroquinolone may be warranted for empirical therapy.**

Rationale For Combination Antimicrobial Therapy

- **Most infections should be treated with a single antimicrobial agent.**

- **Although indications for combination therapy exist, antimicrobial combinations are often <u>overused</u> in clinical practice.**

- **The unnecessary use of antimicrobial combinations increases toxicity and costs and may occasionally result in <u>reduced efficacy</u> due to antagonism of one drug by another.**

Rationale For Combination Antimicrobial Therapy

- **Antimicrobial combinations should be selected for one or more of the following reasons:**

1. **To provide broad-spectrum empiric therapy in seriously ill patients.**

2. **To treat polymicrobial infections (intra-abdominal abscesses, which are due to a combination of anaerobic and aerobic gram-negative organisms, and enterococci).**

Rationale For Combination Antimicrobial Therapy

- The antimicrobial combination chosen should cover the most common known or suspected pathogens but not cover all possible pathogens.

3. To decrease the emergence of resistant strains – tuberculosis.

4. To obtain enhanced inhibition or killing.

Rationale For Combination Antimicrobial Therapy

5. To decrease dose-related toxicity by using reduced doses of one or more components of the drug regimen.

- The use of flucytosine in combination with amphotericin B for the treatment of cryptococcal meningitis in non–HIV-infected patients allows for a reduction in amphotericin B dosage with decreased amphotericin B-induced nephrotoxicity.

Rationale For Combination Antimicrobial Therapy

Broadening the Spectrum of Coverage:

- Increasing the coverage of antimicrobial therapy generally is necessary in the following cases:

1. In mixed infections where multiple organisms are likely to be present (in intra-abdominal and female pelvic infections), in which a variety of aerobic and anaerobic bacteria can produce disease.

- A combination of a drug active against aerobic Gram-negative bacilli (aminoglycoside) and a drug active against anaerobic bacteria (metronidazole or clindamycin) is selected.

Rationale For Combination Antimicrobial Therapy

2. For critically ill patients with presumed health care-associated infections.

- These infections are frequently caused by multi-drug resistant pathogens.

- Combination therapy is used in this setting to ensure that at least one of the antimicrobials will be active against the pathogen(s).

Rationale For Combination Antimicrobial Therapy

Synergism:

- **This is necessary for infections caused by enteric Gram-negative bacilli in immunosuppressed patients.**

- **Traditionally, combinations of aminoglycosides and β-lactams have been used because these drugs together generally act synergistically against a wide variety of bacteria.**

Rationale For Combination Antimicrobial Therapy

- Synergistic combinations appear to produce better results in infections caused by *Pseudomonas aeruginosa* and *Enterococcus* species.

- The most obvious example of the use of synergy is the treatment of enterococcal endocarditis. The causative organism is usually only inhibited by penicillins, but it is killed rapidly by the addition of streptomycin or gentamicin to a penicillin.

Rationale For Combination Antimicrobial Therapy

Preventing Resistance:

- **The use of antimicrobial combinations to prevent the emergence of resistance has been demonstrated in the treatment of tuberculosis.**

- **Combinations of drugs with different mechanisms should be used in this case.**

Disadvantages of Combination Therapy

1. Increased cost.
2. Greater risk of drug toxicity (nephrotoxicity) with aminoglycosides, amphotericin, and vancomycin.
3. Superinfection with more resistant bacteria.
4. Antagonistic effects: when one drug induces β-lactamase production and the other is susceptible to β-lactamase.

- Cefoxitin and imipenem are capable of inducing β-lactamases and may result in more rapid inactivation of penicillins.

Antimicrobial Prophylaxis

- **Antimicrobial agents are effective in preventing infections in many settings.**

- **Antimicrobial prophylaxis should be used in circumstances in which efficacy has been demonstrated and benefits outweigh the risks of prophylaxis. (EBM).**

Antimicrobial Prophylaxis

Surgical Prophylaxis:

- **Surgical wound infections are a major category of nosocomial infections.**

- **Risk factors for postoperative wound infections:**

a) operations on the abdomen.

b) operations lasting more than 2 hours.

c) contaminated or dirty wound.

d) at least three medical diagnoses.

Antimicrobial Prophylaxis

- **Surgical procedures that carry a significant risk of postoperative site infection and necessitate the use of antimicrobial prophylaxis include:**

a) contaminated and clean-contaminated operations.

b) selected operations in which postoperative infection may be catastrophic such as open heart surgery.

c) clean procedures that involve placement of prosthetic materials.

d) any procedure in an immunocompromised host.

National Research Council (NRC) Wound Classification Criteria

Clean: Elective, primarily closed procedure; respiratory, gastrointestinal, biliary, genitourinary, or oropharyngeal tract not entered; no acute inflammation and no break in technique; expected infection rate ≤ 2%.

Clean contaminated: Urgent or emergency case that is otherwise clean; elective, controlled opening of respiratory, gastrointestinal, biliary, or oropharyngeal tract; minimal spillage or minor break in technique; expected infection rate ≤ 10%.

Contaminated: Acute nonpurulent inflammation; major technique break or major spill from hollow organ; penetrating trauma less than 4 hours old; chronic open wounds to be grafted or covered; expected infection rate about 20%.

Dirty: Purulence or abscess; preoperative perforation of respiratory, gastrointestinal, biliary, or oropharyngeal tract; penetrating trauma more than 4 hours old; expected infection rate about 40%.

Antimicrobial Prophylaxis

- **General principles of antimicrobial surgical prophylaxis include the following:**

1. **The antibiotic should be active against common surgical wound pathogens; unnecessarily broad coverage should be avoided.**

2. **The antibiotic should have proved efficacy in clinical trials.**

3. **The antibiotic must achieve concentrations greater than the MIC of suspected pathogens, and these concentrations must be present at the time of incision.**

Antimicrobial Prophylaxis

4. The shortest possible course—ideally a single dose—of the most effective and least toxic antibiotic should be used.

5. The newer broad-spectrum antibiotics should be reserved for therapy of resistant infections.

6. If all other factors are equal, the least expensive agent should be used.

TABLE 51–7 Recommendations for surgical antimicrobial prophylaxis.

Type of Operation	Common Pathogens	Drug of Choice
Cardiac (with median sternotomy)	Staphylococci, enteric gram-negative rods	Cefazolin
Noncardiac, thoracic	Staphylococci, streptococci, enteric gram-negative rods	Cefazolin
Vascular (abdominal and lower extremity)	Staphylococci, enteric gram-negative rods	Cefazolin
Neurosurgical (craniotomy)	Staphylococci	Cefazolin
Orthopedic (with hardware insertion)	Staphylococci	Cefazolin
Head and neck (with entry into the oropharynx)	*Staphylococcus aureus*, oral flora	Cefazolin + metronidazole
Gastroduodenal	*S aureus*, oral flora, enteric gram-negative rods	Cefazolin
Biliary tract	*S aureus*, enterococci, enteric gram-negative rods	Cefazolin
Colorectal (elective surgery)	Enteric gram-negative rods, anaerobes	Oral erythromycin + neomycin[1]
Colorectal (emergency surgery or obstruction)	Enteric gram-negative rods, anaerobes	Cefoxitin, cefotetan, ertapenem, or cefazolin + metronidazole
Appendectomy, nonperforated	Enteric gram-negative rods, anaerobes	Cefoxitin, cefotetan, or cefazolin + metronidazole
Hysterectomy	Enteric gram-negative rods, anaerobes, enterococci, group B streptococci	Cefazolin, cefotetan, or cefoxitin
Cesarean section	Enteric gram-negative rods, anaerobes, enterococci, group B streptococci	Cefazolin

[1]In conjunction with mechanical bowel preparation.

Antimicrobial Prophylaxis

- The selection of vancomycin over cefazolin may be necessary in hospitals with high rates of methicillin-resistant *S. aureus or S. epidermidis infections.*

- The antibiotic should be present in adequate concentrations at the operative site before incision and throughout the procedure.

- Initial dosing is dependent on the volume of distribution, peak levels, clearance, protein binding, and bioavailability.

Antimicrobial Prophylaxis

- **Parenteral agents should be administered during the interval beginning 60 minutes before incision; administration up to the time of incision is preferred.**

- **In cesarean section, the antibiotic is administered after umbilical cord clamping.**

- **If short-acting agents such as cefoxitin are used, doses should be repeated if the procedure exceeds 3–4 hours in duration.**

- **Single-dose prophylaxis is effective for most procedures and results in decreased toxicity and decreased antimicrobial resistance.**

Antimicrobial Prophylaxis

- **Improper administration of antimicrobial prophylaxis leads to excessive surgical wound infection rates.**

Common errors in antibiotic prophylaxis include:

a) selection of the wrong antibiotic.

b) administering the first dose too early or too late.

c) failure to repeat doses during prolonged procedures.

d) excessive duration of prophylaxis.

e) inappropriate use of broad-spectrum antibiotics.

Antimicrobial Prophylaxis

Nonsurgical Prophylaxis:

- Nonsurgical prophylaxis includes:

a) the administration of antimicrobials to prevent colonization and asymptomatic infection

b) the administration of drugs following colonization by or inoculation of pathogens but before the development of disease.

- Nonsurgical prophylaxis is indicated in:

a) individuals who are at high risk for selected virulent pathogens

b) immunocompromised hosts.

TABLE 51–8 Recommendations for nonsurgical antimicrobial prophylaxis.

Infection to Be Prevented	Indication(s)	Drug of Choice	Efficacy
Anthrax	Suspected exposure	Ciprofloxacin or doxycycline	Proposed effective
Cholera	Close contacts of a case	Tetracycline	Proposed effective
Diphtheria	Unimmunized contacts	Penicillin or erythromycin	Proposed effective
Endocarditis	Dental, oral, or upper respiratory tract procedures[1] in at-risk patients[2]	Amoxicillin or clindamycin	Proposed effective
Genital herpes simplex	Recurrent infection ($\geq$ 4 episodes per year)	Acyclovir	Excellent
Perinatal herpes simplex type 2 infection	Mothers with primary HSV or frequent recurrent genital HSV	Acyclovir	Proposed effective
Group B streptococcal (GBS) infection	Mothers with cervical or vaginal GBS colonization and their newborns with one or more of the following: (a) onset of labor or membrane rupture before 37 weeks' gestation, (b) prolonged rupture of membranes (> 12 hours), (c) maternal intrapartum fever, (d) history of GBS bacteriuria during pregnancy, (e) mothers who have given birth to infants who had early GBS disease or with a history of streptococcal bacteriuria during pregnancy	Ampicillin or penicillin	Excellent
Haemophilus influenzae type B infection	Close contacts of a case in incompletely immunized children (> 48 months old)	Rifampin	Excellent
HIV infection	Health care workers exposed to blood after needle-stick injury	Tenofovir/emtricitabine and raltegravir	Good
	Pregnant HIV-infected women who are at $\geq$ 14 weeks of gestation; newborns of HIV-infected women for the first 6 weeks of life, beginning 8–12 hours after birth	HAART[3]	Excellent
Influenza A and B	Unvaccinated geriatric patients, immunocompromised hosts, and health care workers during outbreaks	Oseltamivir	Good

Malaria	Travelers to areas endemic for chloroquine-susceptible disease	Chloroquine	Excellent
	Travelers to areas endemic for chloroquine-resistant disease	Mefloquine, doxycycline, or atovaquone/proguanil	Excellent
Meningococcal infection	Close contacts of a case	Rifampin, ciprofloxacin, or ceftriaxone	Excellent
Mycobacterium avium complex	HIV-infected patients with CD4 count < 75/μL	Azithromycin, clarithromycin, or rifabutin	Excellent
Otitis media	Recurrent infection	Amoxicillin	Good
Pertussis	Close contacts of a case	Azithromycin	Excellent
Plague	Close contacts of a case	Tetracycline	Proposed effective
Pneumococcemia	Children with sickle cell disease or asplenia	Penicillin	Excellent
Pneumocystis jiroveci pneumonia (PCP)	High-risk patients (eg, AIDS, leukemia, transplant)	Trimethoprim-sulfamethoxazole, dapsone, or atovaquone	Excellent
Rheumatic fever	History of rheumatic fever or known rheumatic heart disease	Benzathine penicillin	Excellent
Toxoplasmosis	HIV-infected patients with IgG antibody to *Toxoplasma* and CD4 count < 100/μL	Trimethoprim-sulfamethoxazole	Good
Tuberculosis	Persons with positive tuberculin skin tests and one or more of the following: (a) HIV infection, (b) close contacts with newly diagnosed disease, (c) recent skin test conversion, (d) medical conditions that increase the risk of developing tuberculosis, (e) age < 35 y	Isoniazid or rifampin or isoniazid + rifapentine	Excellent
Urinary tract infections (UTI)	Recurrent infection	Trimethoprim-sulfamethoxazole	Excellent

[1]Prophylaxis is recommended for the following: dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa, and invasive procedure of the respiratory tract that involves incision or biopsy of the respiratory mucosa, such as tonsillectomy and adenoidectomy.

[2]Prophylaxis should be targeted to those with the following risk factors: prosthetic heart valves, previous bacterial endocarditis, congenital cardiac malformations, cardiac transplantation patients who develop cardiac valvulopathy.

[3]Highly active antiretroviral therapy. See http://aidsinfo.nih.gov/ for updated guidelines.