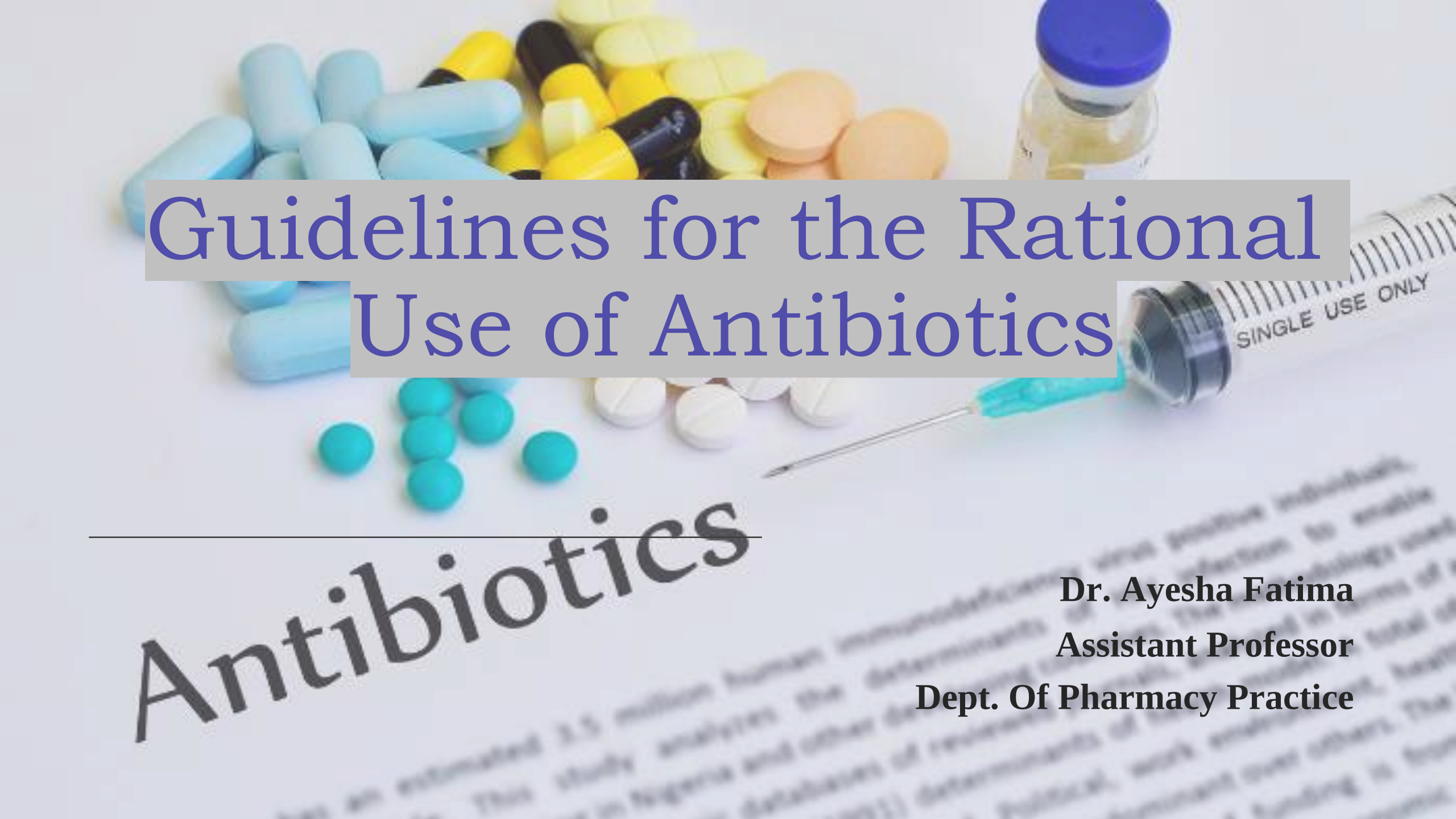




Guidelines for the Rational Use of Antibiotics

Antibiotics

Dr. Ayesha Fatima
Assistant Professor
Dept. Of Pharmacy Practice

- **Antibiotics** : These are substances produced by microorganisms, which selectively suppress the growth of or kill other microorganisms at very low concentrations.
- Chemotherapeutic agent Initially this term was restricted to synthetic compounds, but now since many antibiotics and their analogues have been synthesized, this criterion has become irrelevant; both synthetic and microbiologically produced drugs need to be included together.
- It would be more meaningful to use the term **Antimicrobial agent (AMA)** to designate synthetic as well as naturally obtained drugs that attenuate microorganisms.
- **Rational use of drugs**: Patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and the lowest cost to them and their community.
- **Antimicrobial resistance (AMR)** : Unresponsiveness of a microorganism to an AMA
 - AMR is a global threat today and has overshadowed the potential gain in reducing deaths due to infections. It is estimated that by the year 2050, Asia will have 4.7 million deaths that could be directly attributed to AMR.
 - Antimicrobial resistance is rampant in India with up to 12-59 % of E. coli being extended beta lactamase (ESBL) producers and up to 30% being carbapenemase producers (CP).
 - Klebsiella Pneumoniae has emerged over the last few years as a highly resistant pathogen with up to 50% resistance to carbapenems and rapidly increasing resistance to polymyxins

Antimicrobial Regimen Selection

- Antimicrobials are among the most widely used classes of drugs.
- The use of antibiotics is the main driver in creating selective pressure for the emergence of antimicrobial resistant pathogens; nevertheless, antibiotic overuse remains common.
- Selecting appropriate antimicrobial agent(s) to treat an infection has proven to be a challenging task. Although the choice of a single agent or a combination of agents should be individualized for each patient.

General Principles of antibiotic selection

- ❑ The initial selection of antimicrobial therapy is nearly always empirical, which is prior to documentation and identification of the offending organism.
- ❑ Infectious diseases generally are acute, and a delay in antimicrobial therapy can result in serious morbidity or even mortality.
- ❑ Thus, empirical antimicrobial therapy selection should be based on information gathered from the patient's history and physical examination and results of Gram stains or of rapidly performed tests on specimens from the infected site.
- ❑ This information, combined with knowledge of the most likely offending organism(s) and an institution's local susceptibility patterns, should result in a rational selection of antibiotics to treat the patient.

Systematic Approach for Selection of Antimicrobials

Confirm the presence of infection

- Careful history and physical examination
- Signs and symptoms
- Predisposing factors

Identification of the pathogen

- Collection of infected material
- Stains
- Serologies
- Culture and sensitivity

Selection of presumptive therapy considering every infected site

- Host factors
- Drug factors

Monitor therapeutic response

- Clinical assessment
- Laboratory tests
- Assessment of therapeutic failure

CONFIRMING THE PRESENCE OF INFECTION

- An infectious disease diagnosis is determined by assessing the presence of signs and symptoms of an infection, determining the site of infection, and establishing a microbiological diagnosis, when possible.
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1. **Fever:** *Fever* is defined as a controlled elevation of body temperature above the normal range. The average normal body temperature range taken orally is 36.7°C to 37°C (98°F–98.6°F).
 - The presence of a temperature greater than the expected 37°C (98.6°F) body temperature is considered a hallmark of infectious diseases.
1. **Drug-induced fever** is defined as persistent fever in the absence of infection or other underlying condition. The fever must coincide temporally with the administration of the offending agent and disappear promptly on its withdrawal, after which the temperature remains normal.
 - Possible mechanisms of drug-induced fever are either a hypersensitivity reaction or development of antigen–antibody complexes that result in the stimulation of macrophages and the release of interleukin 1.

4. **local Signs:** The classic signs of pain and inflammation can manifest as swelling, erythema, tenderness, and purulent drainage. These are only visible if the infection is superficial or in a bone or joint.

- The manifestations of inflammation in deep-seated infections (eg, meningitis, pneumonia, endocarditis, and UTI) must be ascertained by examining tissues or fluids.
- For example, the presence of neutrophils in spinal fluid, lung secretions (sputum), or urine is highly suggestive of a bacterial infection.

5. **Symptoms** : Symptoms referable to an organ system must be sought out carefully because not only do they help in establishing the presence of infection, but they also aid in narrowing the list of potential pathogens.

- For example, a febrile patient with complaints of flank pain and dysuria can well have pyelonephritis. In this situation, enteric gram-negative bacilli, especially *Escherichia coli*, are the predominant pathogens.

3. WBC Count : Most infections result in elevated WBC counts (leukocytosis) because of the increased production and mobilization of granulocytes, lymphocytes, or both to ingest and destroy invading microbes.

- The generally accepted range of normal values for WBC counts is between 4,000 and 10,000 cells/mm³.
- Values above or below this range hold important prognostic and diagnostic value.
- Bacterial infections are associated with elevated granulocyte counts, often with immature forms seen in peripheral blood smears. The presence of immature forms (left shift) is an indication of an increased bone marrow response to the infection.
- Because leukocytosis indicates the normal host response to infection, low leukocyte counts after the onset of infection indicate an abnormal response and generally are associated with a poor prognosis.
- The most common granulocyte defect is neutropenia, a decrease in absolute numbers of circulating neutrophils.
- Lymphocytosis, even with normal or slightly elevated total WBC counts, generally is associated with tuberculosis and viral or fungal infections.
- Increases in monocytes can be associated with tuberculosis or lymphoma,
- Increases in eosinophils can be associated with allergic reactions to drugs or infections caused by metazoan.

IDENTIFICATION OF THE PATHOGEN

◦ 1. Microbiological Studies

- Identification and antimicrobial susceptibility of a suspected pathogen are the most important factors in determining the choice of antimicrobial therapy.
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- Infected body materials produced by the patient (eg, blood, Sputum, urine, stool, and wound or sinus drainage), other less accessible fluids or tissues must be obtained if they are suspected to be the infected site (eg, spinal fluid in meningitis and joint fluid in arthritis), must be sampled, if at all possible, or practical, before or concurrently with institution of any antimicrobial therapy for two reasons.
 - First, a Gram stain of the material might reveal bacteria, or an acid fast stain might detect mycobacteria or actinomycetes.
 - Second, the premature use of antimicrobials can suppress the growth of pathogens that might result in false-negative cultures results or alterations in the cellular and chemical composition of infected fluids.
 - Once a microorganism is identified and its susceptibilities are known, specific definitive antimicrobial therapy should be promptly administered.

2. Interpreting Results

- After a positive Gram stain, culture results, or both are obtained, the clinician must be cautious in determining whether the organism recovered is a true pathogen, a contaminant, or a part of the normal flora.
- The normal flora is problematic with cultures obtained from the skin, oropharynx, nose, ears, eyes, throat, and perineum. These surfaces are heavily colonized with a wide variety of bacteria, some of which can be pathogenic in certain settings.
 - For example, coagulase-negative staphylococci are found in cultures of all the mentioned sites, yet are seldom regarded as pathogens unless recovered from blood, venous access catheters, or prosthetic devices.
- For urine cultures, the urinalysis should be used in combination with culture results to assess the presence of WBCs, nitrite, and leukocyte esterase to help confirm infection and rule out colonization.
- Expecterated sputum specimens that must be evaluated carefully by determination of the presence of squamous epithelial cells and leukocytes. A predominance of epithelial cells in sputum specimens reduces the likelihood that recovered bacteria are pathogenic, especially when multiple types of organisms are seen on Gram Stain however sputum evaluation has poor sensitivity and specificity as a diagnostic test.

SELECTION OF PRESUMPTIVE THERAPY

- In many instances, empiric therapy must be instituted before microbiological results are available.
- To select rational antimicrobial therapy for a given clinical situation, a variety of factors must be considered.
- These include the
 - a. severity of the disease,
 - b. local epidemiology and
 - c. antibiogram,
 - d. patient history,
 - e. host factors,
 - f. factors related to the drugs used

1. Antibigram

- Drug choices are influenced by local antimicrobial susceptibility data rather than information published by other institutions or national compilations.
- Each institution should publish an annual summary of antibiotic susceptibilities (antibiogram) for organisms cultured from patients.
- Antibigrams contain both the number of nonduplicate isolates for common species and the percentage susceptible to the antibiotics tested.
- For example, the prevalence of hospital-acquired methicillin resistant *Staphylococcus aureus* (HA-MRSA) in some centers is quite high, whereas in other centers the problem might be nonexistent. This particular situation will influence the selection of therapy for possible *S. aureus* infection, where the clinician must choose either a β -lactam or vancomycin.

2. Patient History

- To define the most likely infecting organisms, a careful history and physical examination must be performed.
- Other questions to ask infected patients regarding the history of present illness include:
 - Are any other people sick at home, especially children?
 - Are any unusual pets kept in the home?
 - Where are you employed (ie, are you exposed to contaminated meat or infectious biohazards)?
 - Has there been any recent travel (ie, to endemic areas of fungal infections or developing countries)?

3. Host Factors

- Several host factors should be considered when evaluating a patient for antimicrobial therapy.
- The most important factors are **drug allergies, age, pregnancy, genetic or metabolic abnormalities, renal and hepatic function, site of infection, concomitant drug therapy, and underlying disease states.**

a. Allergy

- Allergy to an antimicrobial agent generally precludes its use.
- Most commonly cited antimicrobial allergies are those to penicillin, penicillin-related compounds, or both.
- A rule of thumb for giving cephalosporins to patients allergic to penicillin is to avoid giving them to patients who give a good history for immediate or accelerated reactions (eg, anaphylaxis, laryngospasm) and to give them under close supervision in patients with a history of delayed reactions, such as a rash.

b. Age

- The patient's age is an important factor both in trying to identify the likely etiologic agent and in assessing the patient's ability to eliminate the drug(s) to be used.
- The best example of an age determinant of organisms is in bacterial meningitis,
 - For neonates, hepatic and liver functions are not well developed. Therefore, bilirubin excretion is decreased resulting in increased concentration of unconjugated bilirubin that can cause kernicterus. Premature Neonates can develop kernicterus when given sulfonamides.
 - Drug considerations for pediatric patients include low frequency of adverse effects and compliance-enhancing features (eg, absorption not affected by food, once- to twice-daily dosing, and good taste).
- The major physiologic change in persons older than 65 years of age is a decline in the number of functioning nephrons that, in turn, results in decreased renal function.
 - For example, renal toxicity caused by aminoglycosides may be apparent much sooner during therapy in older adults than in younger patients.

c. Pregnancy

- During pregnancy, not only is the fetus at risk for drug teratogenicity, but the pharmacokinetic disposition of certain drugs can be altered.
- Penicillins, cephalosporins, and aminoglycosides are cleared from the peripheral circulation more rapidly during pregnancy.
- The net result is that maternal serum antimicrobial concentrations can be as much as 50% lower during this period than in the nonpregnant state.
- Increased dosages of certain compounds might be necessary to achieve therapeutic levels during late pregnancy

d. Metabolic or Genetic Variation

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

- For example, patients with impaired peripheral vascular flow may not absorb drugs given by intramuscular injection.
- Patients who are phenotypically slow acetylators of isoniazid are at greater risk for peripheral neuropathy.
- Patients with severe deficiency of glucose-6-phosphate dehydrogenase can develop significant hemolysis when exposed to such drugs as sulfonamides, nitrofurantoin, nalidixic acid, antimalarials, and dapsone.

e. Organ Dysfunction

- Patients with diminished renal or hepatic function or both will accumulate certain drugs unless the dosage is adjusted.
- Significant accumulation can occur when both liver dysfunction and renal dysfunction are present for the following drugs: cefotaxime, nafcillin, piperacillin, and sulfamethoxazole.

f. Concomitant Drugs Use

- Any concomitant therapy that the patient is receiving can influence the drug selection, dose, and monitoring.
 - For instance, administration of isoniazid to a patient who is also receiving phenytoin can result in phenytoin toxicity secondary to inhibition of phenytoin metabolism by isoniazid.

g. Concomitant Disease States

- Concomitant disease states can influence the selection of therapy.
 - For example, patients with diabetes mellitus and the resulting peripheral vascular disease often develop infections of the lower extremity soft tissue. the alterations in peripheral blood flow associated with the disease and altered immunity make such infections more difficult to treat than in nondiabetics.

4. Drug Factors

Pharmacokinetic and Pharmacodynamic Considerations

- Integration of both pharmacokinetic and pharmacodynamic properties of an agent is important when choosing antimicrobial therapy to ensure efficacy and to prevent resistance.
- There is an important relationship between both pharmacokinetic and microbiologic parameters that has resulted in measurements such as AUC(Area under Curve)Minimal inhibitory concentration (MIC) ratio and time (T) the concentration is above MIC ($T > MIC$).
- Effective dosing regimens require serum drug concentrations to exceed the MIC for at least 40% to 50% of the dosing interval.

4. Tissue Penetration

- The importance of tissue penetration varies with site of infection.
- The CNS is one body site where antimicrobial penetration is relatively well defined, by CSF concentrations of antimicrobial agents necessary to cure bacterial meningitis, and drugs that do not reach significant concentrations in the CSF should be either avoided or instilled directly, if feasible.
- The proper route of administration for an antimicrobial depends on the site of infection.

5. Drug Toxicity

- It is incumbent on health professionals to avoid toxic drugs whenever possible.
- Antibiotics associated with CNS toxicities, usually when not dose-adjusted for renal function, include penicillins, cephalosporins, quinolones, and imipenem.
- Hematologic toxicities generally are manifested 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).
- 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.

6. Combination Antimicrobial Therapy

- In selecting a drug regimen for a given patient, consideration must be given to the necessity of using more than one drug.
- Combinations of antimicrobials generally are used to broaden the spectrum of coverage for empirical therapy, achieve synergistic activity against the infecting organism, and prevent the emergence of resistance.

8.Synergism

- ❖ The achievement of synergistic antimicrobial activity is advantageous for infections caused by enteric gram-negative bacilli in immunosuppressed patients.
- ❖ Combinations of aminoglycosides and β -lactams have been used because these drugs together generally act synergistically against a wide variety of bacteria.
- ❖ 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.

9. Disadvantages of Combination Therapy

- ❖ potential disadvantages, include increased cost, greater risk of drug toxicity such as nephrotoxicity with aminoglycosides, amphotericin, and possibly vancomycin, and superinfection with even more resistant bacteria.
- ❖ The combination of two or more antibiotics can result in antagonistic effects.
- ❖ For example, the effect of antagonism may be evident when one drug induces β -lactamase production and another drug is β -lactamase unstable. Cefoxitin and imipenem are examples of drugs capable of inducing β -lactamases and may result in more rapid inactivation of penicillins when used together

MONITORING THERAPEUTIC RESPONSE

- ❖ After antimicrobial therapy has been instituted, the patient must be monitored carefully for a therapeutic response.
- ❖ 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.
- ❖ The WBC count and temperature should start to normalize.
- ❖ Physical complaints from the patient also should diminish (ie, decreased pain, shortness of breath, cough, or sputum production).
- ❖ Appetite should improve. However, radiologic improvement can lag behind clinical improvement.

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- ❖ As patients improve clinically, the route of administration should be reevaluated.
 - ❖ Streamlining therapy from parenteral to oral (switch therapy) has become an accepted practice for many infections.
 - ❖ Criteria that should be present to justify a switch to oral therapy include
 - (a) overall clinical improvement,
 - (b) lack of fever for 8 to 24 hours,
 - (c) decreased WBC count, and
 - (d) a functioning GI tract.

FAILURE OF ANTIMICROBIAL THERAPY

- ❖ A variety of factors may be responsible for an apparent lack of response to therapy.
 - It is possible that the disease is not infectious or is nonbacterial in origin, or there is an undetected pathogen in a polymicrobial infection.
 - Other factors include those directly related to drug selection, the host, or the pathogen.
 - Laboratory error in identification, susceptibility testing, or both (presence of inoculum effect or resistant subpopulations) is a rare cause of antimicrobial failure.

1. Failures Caused by Drug Selection

- ❖ Factors related directly to the drug selection include
 - Inappropriate drug selection, dosage, or route of administration.

 - Malabsorption of a drug product because of GI disease (such as a short-bowel syndrome) or
 - Drug interaction
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- ❖ A common cause of failure of therapy is poor penetration into the site of infection. This is especially true for sites such as the CNS, eye, and prostate gland.
 - ❖ Drug failure also can result from drugs that are highly protein bound or that are chemically inactivated at the site of infection.

2. Failures Caused by Host Factors

- ❖ Host defenses must be considered when evaluating a patient who is not responding to antimicrobial therapy.
- ❖ Patients who are immunosuppressed (eg, granulocytopenia from chemotherapy or AIDS) may respond poorly to therapy because their defenses are inadequate to eradicate the infection despite seemingly adequate drug regimens.
- ❖ Other host factors are related to the need for surgical drainage of abscesses or removal of foreign bodies, necrotic tissue, or both.

3. Failures Caused by Microorganisms

There are **two types of resistance**, intrinsic and acquired resistance.

1. **Intrinsic resistance** is when the antimicrobial agent never had activity against the bacterial species.

- For example, gram-negative bacteria are naturally resistant to vancomycin because the drug cannot penetrate the outer membrane of gram negative bacteria.

2. **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.

The strategies used by bacteria to develop acquired resistance are primarily classified into four general mechanisms of resistance:

- (a) alteration in the target site,
- (b) change in membrane permeability,
- (c) efflux pump, and
- (d) drug inactivation.

A single mechanism of resistance can result in resistance to multiple related or unrelated classes of antibiotics.

The increase in resistance among bacteria is a result of

- continued overuse of antimicrobials in the community, as well as in hospitals, a
- the increasing prevalence of immunosuppressed patients
- receiving long-term suppressive antimicrobials for the prevention of infections.

These resistance patterns are regionally variable, and susceptibility patterns in the community (or hospital) should be monitored closely to promote rational antimicrobial selection.