RATIONAL ANTIBIOTIC THERAPY, MANAGEMENT OF SIDE EFFECTS AND WAYS TO AVOID ANTIBIOTIC RESISTANCE

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Abstract:

Antibiotics remain a cornerstone of modern medicine, yet their widespread and often inappropriate use has led to significant challenges, including the emergence of antibiotic resistance and an increased incidence of drug-related side effects. This article explores the

principles of rational antibiotic therapy, focusing on optimizing drug selection, dosage, and duration to maximize efficacy while minimizing adverse outcomes. Additionally, we introduce common side effects associated with antibiotics, discussing both pharmacological and clinical management strategies to mitigate these reactions. Importantly, the paper also addresses the growing global concern of antibiotic resistance, emphasizing the need for stringent antimicrobial stewardship programs and the development of novel approaches to prevent resistance. Preventative strategies, such as antibiotic rotation, patient education, and the promotion of infection prevention measures, are also considered. Through a comprehensive understanding of antibiotic therapy, healthcare professionals can improve patient outcomes while curbing the threat of antibiotic resistance.

Main part:

Antibiotics, also known as antibacterial agents, are medications derived from microorganisms or fungi used to treat and prevent bacterial infections. They can either kill bacteria or inhibit their growth, and some also have effects against protozoa. However, antibiotics are ineffective against viruses and can be harmful when misused.

Inappropriate or irrational use of these medications can be identified through several clinical criteria, including:

1. Prescribing the same active ingredient under multiple trade names.
2. Concurrently prescribing interchangeable or drugs from the same pharmacological group.
3. Combining medications that are categorically incompatible.
4. Including more than two antibiotics in a single prescription (via the same route).
5. Prescribing medications that may worsen existing conditions.

In 2008, a group of 19 experts from 13 European countries established the "START/STOPP" criteria in Ireland, which were updated in 2015 to enhance the effectiveness of medication combinations. These criteria aim to audit medicinal products in both outpatient and inpatient settings, ensuring effective treatment, especially for elderly patients over 65 who often have multiple health issues. The recommendations provided are based on strong scientific evidence regarding the risks associated with various drugs in clinical practice.

It is now understood that using broad-spectrum antibiotics, high doses, or combinations of antibiotics is not always necessary for effective treatment. Instead, accurate, targeted antimicrobial therapy is essential, with the identification of the infectious agent and its sensitivity being key. Combining antibiotics with antipyretics, sedatives, or glucocorticoids is not always warranted.

Currently, antibiotic resistance poses a significant challenge in treating various infections. Key factors contributing to resistance include the production of enzymes that deactivate antibiotics, structural changes in bacterial targets, drug expulsion via specific transporters, and reduced

permeability of bacterial cell membranes. Strategies to combat resistance include using adjuvants to prevent antibiotic inactivation or employing antibiotic combinations.

Empiric antibiotic therapy is initiated to address infections requiring urgent medical intervention prior to the identification of specific pathogens. Prior to commencing such therapy, it is essential to establish a clinical diagnosis, which involves obtaining samples for laboratory analysis, confirming a microbiological diagnosis, and determining the necessity of initiating treatment before laboratory results are available. Furthermore, the selection of the most appropriate antimicrobial agent or combination thereof must be made. A wealth of scientific literature and digital resources provide comprehensive guidance on the optimal antimicrobial agents for targeting specific pathogens.

For established infections, antimicrobial therapy is guided by the following principles: conducting a sensitivity test to identify the most effective agent, assessing the drug's bioavailability (i.e., its concentration in the bloodstream), selecting the appropriate route of administration, monitoring the therapeutic response, and considering the potential for clinical ineffectiveness of the antimicrobial treatment.

Antibiotics are classified into two main categories: bacteriostatic and bactericidal agents. Bacteriostatic antibiotics, such as clindamycin, macrolides, sulfonamides, and tetracyclines, inhibit bacterial growth at concentrations significantly lower than those required to kill bacteria. Bactericidal antibiotics, which include aminoglycosides, beta-lactam antibiotics, fluoroquinolones, metronidazole, streptogramins, and vancomycin, have minimal difference between the concentration needed to inhibit bacterial growth and the concentration required to kill bacteria. Bactericidal agents are preferred for the treatment of severe infections like endocarditis and meningitis, as well as in immunocompromised patients.

The principles of antibiotic combination therapy have been well-established, focusing on the bacteriostatic or bactericidal effects on the pathogen. It is generally not recommended to combine bactericidal antibiotics with bacteriostatic ones. For example, the combined use of chloramphenicol (levomycetin) and penicillin in treating meningococcal infections in children has been associated with increased mortality compared to monotherapy with either drug alone. If a microorganism is more sensitive to a bacteriostatic antibiotic, synergism between the antibiotics may occur. However, if it is more sensitive to a bactericidal antibiotic, antagonism is more likely to develop, where the bacteriostatic antibiotic can reduce the effectiveness of the bactericidal agent.

Bactericidal agents such as aminoglycosides and fluoroquinolones exhibit concentration-dependent killing, which is why high doses are often required to achieve full clinical effectiveness. In contrast, other bactericidal agents like beta-lactams and vancomycin demonstrate time-dependent killing, where their bactericidal effect is not influenced by increasing concentrations, provided the drug concentration remains above the minimum bactericidal concentration (MBC).

Postantibiotic Effect: This refers to the reduction in bacterial growth that continues even after antibiotic levels in the bloodstream drop below the minimum required to inhibit bacterial growth. The postantibiotic effect is an important consideration for the effectiveness of aminoglycosides when used alone, as well as for the clinical efficacy of fluoroquinolones.

Changes in liver and kidney function, along with dialysis treatment, can influence how antibiotics are eliminated from the body, which may necessitate adjustments in dosage.

In cases of anuria (where creatinine clearance is less than 5 mL/min), the half-life of antibiotics eliminated through the kidneys may significantly increase, requiring a reduction in dosage. Antibiotics such as erythromycin, clindamycin, chloramphenicol, rifampin, and ketoconazole do not need dose adjustments in patients with renal impairment. Certain antimicrobials are contraindicated in renal failure, including cidofovir, nalidixic acid, long-acting sulfonamides, and tetracyclines.

In cases of liver dysfunction, dosage adjustments are also necessary for drugs primarily cleared by the liver, such as amprenavir, chloramphenicol, clindamycin, erythromycin, indinavir, metronidazole, and tigecycline. Drugs that are not removed by hemodialysis include amphotericin B, cefoperazone, ceftriaxone, erythromycin, nafcillin, tetracyclines, and vancomycin.

- Vancomycin - effective against gram-positive infections. Especially often used for methicillin-resistant Staphylococcus aureus, Clostridium difficile-enterocolitis.

Side effects: hyperemia (red man syndrome), ototoxicity (rar but should be prescribed carefully with drugs characterized by ototoxicity, such as aminoglycosides), nephrotoxicity, phlebitis at the injection site.

Pharmacokinetics: poorly absorbed by the gastrointestinal tract.

- Sulfonamides - effective against gram-positive and gram-negative bacteria: Nocardia, Chlamydia trachomatis, some protozoa (malaria), E. coli, Klebsiella, Salmonella, Shigella, Enterobacter.

Side effects: nausea, vomiting, diarrhea, phototoxicity, hemolysis (in individuals with glucose-6-phosphate dehydrogenase deficiency) hypersensitivity, Steven-Johnson syndrome (the frequency and severity of these events are increased in immunocompromised individuals with AIDS).

Sulfonamides in newborns- expelling bilirubin from albumin, as a result causes jaundice (kernicterus), also expelling warfarin and methotrexate.

Pharmacokinetics: mostly orally active drugs; characterized by hepatic and renal clearance

- Trimethoprim-sulfamethoxazole combination – effective against urinary tract infections caused by E. coli, as well as against upper respiratory tract infections such as Pneumocystis jiroveci pneumonia, some non-tuberculous mycobacterial infections, as well as S. Aureus, Haemophilus sp, Moraxella catarrhalis and Klebsiella pneumoniae, urinary tract infections and upper respiratory tract infections.

Side effects: fever, erythema, bone marrow suppression, hyperkalemia
Pharmacokinetics: oral and IV active, characterized by renal clearance.

- Fluoroquinolones- effective against many gram-positive and gram-negative bacteria - Shigella, Salmonella, E. Coli, Campylobacter, Pseudomonas, Enterobacter. Used for cases of chlamydial urethritis or cervicitis and atypical microbacteria

Side effects: nausea, vomiting and diarrhea –are the most common negative effects. Others include - drowsiness or insomnia, headache, photosensitivity, prolongation of the QT interval. Gatifloxacin causes hyperglycemia in diabetic patients and hypoglycemia when used in combination with other hypoglycemic drugs; Suppression of the development of cartilage, as a result the risk of tendon rupture and tendonitis increases.
Pharmacokinetics: oral and IV active, more characterized by renal clearance.

- Aztreonam- It is the only monobactam used in the US against aerobic gram-negative rods, including pseudomonas.

Monobactams are drugs of choice in patients who are allergic to penicillins and also used for gram-negative infections.

- Beta-lactamase-sensitive, narrow-spectrum antibiotics: penicillin G (IV), penicillin V (perorally).

Activity: Penicillin G - streptococci, meningococci, gram-positive bacilli and spirochetes; Activity against enterococci increases when combined with aminoglycosides.
Penicillin V is active in oropharyngeal infections

- Wide spectrum sensitive to beta-lactamase: amoxicillin, ampicillin, piperacillin, ticarcillin

Activity: Ampicillin is synergistic with aminoglycosides in enterococci, listeria monocytogens, Escherichia coli, Proteus mirabilia, Haemophilus influenzae, Moraxella catarrh, enterococcal and listerial infections.

- Piperacillin and ticarcillin - Active against various gram-negative strains, pseudomonas, enterobacteria, Klebsiella; Activity increases when combined with penicillinase inhibitors (tazobactam and clavulic acid). Ampicillin is used for pseudomembranous colitis.

Side effects of penicillin: Urticaria, fever, hemolytic anemia, nephritis, anaphylaxis;
Meticillin causes - interstitial nephritis; Nafticillin - neutropenia;
Ampicillin - maculopapular rash on the skin, heart palpitations, vomiting.

- Antistaphylococcal antibiotics – Meticillin, Oxacillin, Nafcilin

Parenteral penicillins: Ampicillin, Ticarcillin, piperacillin. Penicillins are eliminated by Glomerular filtration and tubular excretion in an unchanged form in urine, which is inhibited by uricosuric agents with probenicid.
Ampicillin and nafcilin are excreted in the bile; Most penicillins pass through the blood-brain barrier, when there is an inflammation in the brain (meningitis, encephalitis).

- Beta-lactamase inhibitors: Sulbactam, Clavulinic acid, Tazobactam

Active against gonococci, streptococci, E coli and H influenzae strains that produce beta-lactamases.

less active against chromosomal beta-lactamases produced by enterobacteria, seratia and pseudomonas strains.

- First Generation (e.g., cefazolin, cephalexin) - Spectrum: Primarily effective against gram-positive bacteria.

Uses: Treats skin and soft tissue infections, as well as infections caused by E. coli and K. pneumoniae.

Side Effects: Hypersensitivity reactions, gastrointestinal issues.

Pharmacokinetics: Available in oral and IV forms; eliminated through renal clearance.

- Second Generation (e.g., cefaclor, cefotetan, cefoxitin) - Spectrum: Increased activity against gram-negative bacteria, reduced effectiveness against gram-positive bacteria.

Uses: Effective against anaerobes like Bacteroides fragilis, and respiratory infections caused by H. influenzae or M. catarrhalis.

Side Effects: Similar to first generation.

Pharmacokinetics: Administered orally and IV; eliminated by renal clearance.

- Third Generation (e.g., cefotaxime, ceftriaxone, ceftazidime) - Spectrum: Primarily targets gram-negative bacteria and penetrates the blood-brain barrier; not resistant to beta-lactamases.
- Fourth Generation (e.g., cefepime, ceftaroline) - Spectrum: Broadest spectrum and resistant to beta-lactamases produced by gram-positive strains; effective against penicillin-resistant pneumococci and methicillin-resistant Staphylococcus aureus (MRSA).

Side Effects: Similar to earlier generations, with added risks of nephrotoxicity and bleeding issues (hypoprothrombinemia).

Pharmacokinetics: Available in oral and IV forms; eliminated renally.

- Aminoglycosides - Effectiveness: More effective in a single high dose; their antibacterial effect lasts longer than measurable blood concentration.

Spectrum: Primarily against gram-negative bacteria.

Side Effects: Nephrotoxicity, ototoxicity, hypersensitivity, and neuromuscular blockade (monitoring necessary).

Synergy: They work well with penicillins but should not be combined due to inactivation issues.

- Clindamycin - Effectiveness: Targets gram-positive bacteria, MRSA, and anaerobes; used in patients allergic to penicillins.

Side Effects: Can cause pseudomembranous colitis.

Pharmacokinetics: Orally active, metabolized extensively, and excreted in bile.

- Macrolides - Effectiveness: Effective against corynebacteria and chlamydial infections; azithromycin is preferred for chlamydia due to its long half-life.

Side Effects: Hepatotoxicity, gastrointestinal issues, QT prolongation, and interactions with CYP450 enzymes.

Pharmacokinetics: Administered orally and IV.

- Tetracyclines (e.g., minocycline, doxycycline) - Effectiveness: Effective against a variety of infections including chlamydia and H. pylori; also used for acne and in SIADH treatment.

Side Effects: Gastrointestinal issues, hepatotoxicity, photosensitivity, and potential for superinfection.

Pharmacokinetics: Administered orally and IV; clearance varies by drug.

- Chloramphenicol - Effectiveness: Broad-spectrum, often reserved for specific cases.

Side Effects: Gray baby syndrome in neonates, aplastic anemia, and gastrointestinal disturbances.

Pharmacokinetics: Administered orally and intravenously; eliminated hepatically.

- Streptogramins (Quinopristin, Dalfopristin): These antibiotics are effective against staphylococcal infections, vancomycin-resistant enterococci (VRE), and MRSA. Common side effects include arthralgia and myalgia. They interact with several CYP450 enzymes, acting as inhibitors. Pharmacokinetically, they are administered intravenously and eliminated via renal clearance.
- Oxazolidinones (Linezolid, Tedizolid): Effective against Gram-positive bacteria, including MRSA and penicillin-resistant Streptococcus pneumoniae (PRSP), particularly for skin and soft tissue infections. Side effects can include dose-dependent anemia, neuropathy, and optic neuritis, as well as the risk of serotonin syndrome when used with SSRIs. They can be given orally or intravenously and are metabolized by the liver. Tedizolid is long-acting, requiring only once-daily dosing.
- Daptomycin (Cyclic Lipopeptide Antibiotic): This antibiotic is used for Gram-positive organisms, including for endocarditis and sepsis, and is effective against VRE and staphylococci. Side effects include myopathy, and monitoring of creatine phosphokinase is recommended weekly. It is primarily eliminated by the kidneys.
- Rifamycins (Bactericidal - Rifampin, Rifabutin, Rifapentine): These are primarily antituberculosis antibiotics. Side effects may include flu-like symptoms, hepatitis, elevated liver function tests, proteinuria, and thrombocytopenia, along with a reddish-orange discoloration of tears, sweat, and urine. They act as inducers of cytochrome P-450 enzymes. Rifampin can be administered orally or intravenously, while the others are typically given orally; all are eliminated by the liver.
- Polymyxins (Bactericidal, Colistin): Effective against Gram-negative bacteria (e.g., Acinetobacter, Escherichia coli, Pseudomonas aeruginosa), they are used for lower respiratory and urinary tract infections, especially in cystic fibrosis patients. Side effects can include

hypersensitivity reactions and nephrotoxicity. Colistin is administered intravenously and requires renal function assessment before use due to its renal clearance.

- Pregnancy and Newborn Considerations: Antimicrobial therapy during pregnancy and in newborns necessitates careful approaches. Aminoglycosides can cause neurological issues, while tetracyclines may lead to enamel dysplasia and delayed bone growth. Sulfonamides can displace bilirubin from serum albumin, resulting in kernicterus in newborns. Chloramphenicol may cause "gray baby" syndrome. Most antiviral and antifungal medications are contraindicated during pregnancy. Fluoroquinolones are not recommended for pregnant women or children due to potential harm to cartilage development.
- Important Antibiotic Interactions: Drug interactions may alter the effectiveness of medications, manifesting as either pharmacodynamic (additive, synergistic, or antagonistic effects) or pharmacokinetic interactions. Pharmaceutical interactions can occur when drugs are administered simultaneously, leading to potential incompatibilities. Drug-drug interactions can reduce or enhance the effects of medications and may result in adverse effects.
- Drug Interaction Issues During Antibiotic Therapy: Certain antibiotics can increase nephrotoxicity or ototoxicity when combined with other drugs. For example, aminoglycosides can have enhanced toxicity when used with loop diuretics, vancomycin, or cisplatin. Sulfonamides may compete with other drugs for plasma protein binding, increasing the risk of hypoglycemia when used with sulfonylureas or enhancing hypoprothrombinemia when combined with warfarin. Disulfiram-like reactions may occur when combined with ethanol, particularly with sulfonamides, cephalosporins, and metronidazole.
- Erythromycin can inhibit the metabolism of several drugs, including clozapine and warfarin, increasing their plasma concentrations. Ketoconazole affects the metabolism of caffeine, statins, and other medications. Other antifungal azoles have minimal impact on drug metabolism.
- Antacids can interact with fluoroquinolones and tetracyclines, reducing their gastrointestinal absorption. Carbamazepine may decrease the plasma concentration of doxycycline. Disulfiram and cephalosporins can cause disulfiram-like reactions with ethanol, while erythromycin can suppress the metabolism of carbamazepine and increase the risk of toxicity for other drugs. Phenytoin can lower the plasma levels of doxycycline, while rifampin can enhance the effectiveness of sulfanilamides.

Antibiotics are one of the most frequently used drugs, but as a result of their interaction with food products, their effectiveness can increase or toxic effects can develop; It is not recommended to take antibiotics with milk and milk products, since they are a source of divalent ions – calcium and magnesium, which form a complex with antibiotics and inhibit their absorption.

According to various studies, it was substantiated that fluoroquinolones form easily soluble complexes with metals contained in food, as a result of which their bioavailability decreases; Casein and calcium contained in milk reduce the absorption of ciprofloxacin.

When taking tetracyclines, it is necessary to avoid the use of milk and milk-containing products, as well as, fruits that contain a large amount of calcium, in order to prevent the formation of insoluble complexes;

When combining different antimicrobial agents, the following clinical conditions should be taken into account:

1. Emergency situations — severe infections (for example, sepsis, meningitis), when a combination of antimicrobial agents is used empirically to suppress all possible pathogens;
2. For the prevention of resistance — the use of a combination of antimicrobial agents to avoid resistance, so that antimicrobial therapy is effective; This approach is often used in the treatment of tuberculosis;
3. Mixed infections — development of potentially dangerous infections caused by different pathogens. For example, in the development of peritonitis, it is possible that different microbes took part (for example, anaerobes and coliforms); In this case, combined antimicrobial therapy should cover the mentioned microbes; Also, in case of skin infections, antibacterial, antifungal and antiviral agents are often used at the same time.

Synergistic effect is indicated when 2 or 3 antibiotics are combined and their individual effects are summed up; For example: use of penicillin with gentamicin in case of enterococcal endocarditis; Use of penicillin + aminoglycoside in case of Pseudomonas aeruginosa; Combined use of vancomycin + rifampin against penicillin-resistant pneumococci.

Basic antimicrobial chemoprophylaxis principles are that: Prophylaxis should always be directed against a specific pathogen; The development of resistance should be excluded; Preventive pharmacotherapeutic intervention should be time-limited and clearly defined, as well as in the case of the dosage regimen; Prophylaxis should be justified by high-quality evidence and taking into account the individual characteristics of the patient.

There are various ways to avoid medicinal iatrogeny, such as : Sufficient knowledge of indications, contraindications, side effects of medication use; limiting self-medication and reducing overuse of medications; introduction of qualified systematic training programs for doctors and other medical personnel; Consultation with a clinical pharmacologist at any stage of treatment, which will help a doctor of any specialty to minimize the complications caused by polypharmacy and the use of inappropriate drugs. The risk/benefit ratio of prescribed drugs can be improved by proper knowledge of the patient's medical history and side effects of the drugs.

Selection of optimally effective medicine can be achieved by successfully identifying the Pathogen; by considering the age, gender and accompanying diseases of the patient, as well as, the possibility and danger of potential interactions with other drugs.

The secret of Good Prescribing lies in selecting the most effective and harmless drug; Justification of the choice - motivation; and of course Knowledge of clinical pharmacology and rational pharmacotherapy approaches.

The selection of a personal drug for a particular patient is preceded by a complex process, which involves the compatibility of the drug with the patient.

Factors contributing to the development of side effects of drugs:

- Pregnancy -Teratogenic, embryotoxic and fetotoxic effect.
- Lactation- possible effect of the drug on the body of the breastfed child.
- Kidney function disorder- Toxic action of the drug due to its slow release from the body (reduced clearance).
- Liver function disorder - drug-induced hepatotoxicity
- Drug allergy -Allergic reaction to the drug, which develops as a result of its administration.

Conclusion:

In conclusion, rational antibiotic therapy is essential to maintaining the efficacy of these drugs while mitigating the risks of adverse effects and the development of antibiotic resistance. By carefully selecting appropriate antibiotics, optimizing dosages, and tailoring treatment duration, healthcare professionals can maximize therapeutic outcomes and minimize unnecessary harm to patients. Antimicrobial stewardship, combined with preventative strategies such as antibiotic rotation, patient education, and infection control measures, is vital in curbing the global threat of resistance. Through a concerted effort to apply these principles, the medical community can safeguard antibiotic effectiveness for future generations, ensuring these life-saving drugs remain a cornerstone of healthcare.

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