

## REVIEWS

# ANTIMICROBIAL THERAPY: GENERAL PRINCIPLES AND RECOMMENDATIONS FOR GOOD MEDICAL PRACTICE. A REVIEW

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## ABSTRACT

**INTRODUCTION:** The terms *antimicrobial* and *antibiotic* refer to various therapeutic agents, including antibacterial, antiviral, antifungal, and antiparasitic drugs. Many factors should be considered before prescribing any of these pharmaceutical agents. Some factors are related to the etiologic agents and their behavior, while others are patient-related and depend on individual characteristics.

**AIM:** This review aims to identify the critical aspects of antimicrobial drug therapy, such as appropriate timing, duration, regimens, interpretation of antimicrobial susceptibility testing (AST) results, patient-related factors, and antimicrobial resistance (AMR).

**MATERIALS AND METHODS:** An electronic search was performed in PubMed, Scopus, Web of Science, and Google Scholar, using the following keywords: (((antimicrobial) OR (antibiotic)) AND ((treatment) OR (therapy)) AND (principles) AND ((antimicrobial) AND (resistance))). After evaluation and analysis of the obtained data, 33 articles were included in this study.

**RESULTS:** The first step in antimicrobial therapy is selecting an appropriate drug and regimen. The diagnosis is determined by careful analysis of the site of infection, the patient's general and immune status, and the establishment of the microbial agent. The timing of the antimicrobial therapy depends on the urgency. In high-risk patients, empiric treatment should start immediately after collecting specimens for culture and sensitivity testing. Patient-related factors that should be considered when selecting antimicrobial therapy are hepatic and renal function, age, genetic susceptibility, allergies, pregnancy, lactation, and prior antibiotic use.

**CONCLUSION:** Antimicrobial therapy should be based on selecting appropriate pharmaceutical agents and doses, route of administration, timing, and duration of the treatment. Numerous etiologic and patient-related factors should be considered during the treatment. The growing risk of AMR requires more cautious behavior and strict following of the recommendations for good medical practice.

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**Keywords:** *antimicrobial, antibiotic, treatment, therapy, principles, resistance*

**Received:** October 27, 2024

**Accepted:** December 2, 2024



## INTRODUCTION

The terms *antimicrobial* and *antibiotic* refer to various therapeutic agents, including antibacterial, antiviral, antifungal, and antiparasitic drugs. Many factors should be considered before prescribing any of these pharmaceutical agents. Some factors are related to the etiologic agents and their behavior, while others are patient-related and depend on individual characteristics. The classification of these drugs depends on the class and spectrum of the targeted microorganisms, the biochemical pathway of the agent, and its chemical structure (1). The selection of an appropriate antimicrobial agent is based on the known or likely pathogens responsible for the condition, the antimicrobial spectrum of the drug, and its pharmacokinetic and pharmacodynamic characteristics (2,3). Major aspects of antimicrobial prescription are the dose, route, and duration of the treatment. The prescription of inappropriate or unnecessary antibacterial drugs must be avoided as society faces an era of an increasing and intimidating antimicrobial resistance (AMR). The World Health Organization defines AMR as one of the ten global public health threats (4). The widespread antibiotic misuse and overuse suggest that, although the basic principles of antibiotic prescription have been long known, they should be repeatedly presented to the medical society. Awareness should be raised regarding the devastating effects of their overprescription. Good medical practice in antimicrobial prescription is a key prerequisite for effectively managing infectious diseases (2).

## AIM

This review aims to identify the critical aspects of antimicrobial drug therapy, such as appropriate timing, duration, regimens, interpretation of antimicrobial susceptibility testing (AST) results, patient-related factors, and AMR.

## MATERIALS AND METHODS

An electronic search was performed on 4 December 2024 in PubMed, Scopus, Web of Science, and Google Scholar, using the following keywords: (((antimicrobial) OR (antibiotic)) AND ((treatment) OR (therapy)) AND (principles) AND ((antimicrobial) AND (resistance))). The inclusion criteria were articles that discussed the general principles of antimicrobial therapy regarding regimens, timing, dura-

tion, mechanisms of action, etc. After evaluation and analysis of the obtained data, 33 articles were included in this study.

## RESULTS AND DISCUSSION

The first step in antimicrobial therapy is selecting an appropriate drug and regimen. The diagnosis is determined by careful analysis of the site of infection, the patient's general and immune status, and the establishment of the microbial agent, if possible. In cases of serious life-threatening infections and when prolonged antimicrobial therapy is expected, the specific etiological agent should be isolated (1). If the selected therapy is ineffective, additional testing will be necessary to identify the pathogen. Ideally, the causative agent is identified by microbial culture or serologic testing (5). However, in most cases, the most likely pathogen is suspected from the clinical findings.

The timing of the antimicrobial therapy depends on the urgency. In high-risk patients, empiric treatment should start immediately after collecting specimens for culture and sensitivity testing (1,6). Premature initiation of the therapy in such cases can cause difficulties in disease management. In stable patients, especially when prolonged treatment duration is expected, antimicrobial therapy can start after establishing microbiological diagnosis. Microbiological results usually take 1–3 days. Therefore, the initial therapy is often empirical with broad-spectrum antibiotics in order to cover multiple possible agents (1).

Empirical antibiotic therapy should be based on the site of infection and the most possible etiological agents, previous anamnesis for microbial infections, and local microbial resistance (7).

The antimicrobial spectrum should be narrowed when the pathogen and its antimicrobial susceptibility are identified. Thus, the risk of AMR, treatment cost, and toxicity can be reduced (1).

Antimicrobial susceptibility testing (AST) assesses the ability of pathogens to grow in the presence of specific pharmaceutical agents. The standards for AST are established by the Clinical and Laboratory Standards Institute (8). The rationale for performing AST is to predict the efficacy of certain antimicrobial drugs. Data are presented in minimum inhibitory concentration (MIC)—the lowest drug con-

centration that inhibits microbial growth. Microorganisms are classified as susceptible, intermediate, or resistant (9). When evaluating the AST results, the site of infection should be considered as some pathogens can be susceptible to a specific antimicrobial drug but the drug may be incapable of reaching therapeutic concentrations at the site of infection. Furthermore, some microorganisms release enzymes in vivo that inactivate the drugs they show in vitro susceptibility to. An example of such enzymes is the extended-spectrum  $\beta$ -lactamases (1,10).

Another significant aspect of antibacterial drugs is their mechanism of action—bactericidal or bacteriostatic. Bactericidal agents disrupt the cell wall, membrane, or DNA and destroy the bacteria. Bacteriostatic drugs inhibit different synthesis processes necessary for bacterial replication. Some bactericidal agents can be bacteriostatic for some microorganisms and some bacteriostatic drugs can demonstrate bactericidal properties in higher concentrations (11).

Some cases necessitate antibiotic combinations, such as high-risk patients before the microbiological and AST results, polymicrobial infections, and high risk of resistance.

It has been suggested that antibiotic combinations with synergistic activity provide a greater effect than their independent action, e.g.,  $\beta$ -lactams and aminoglycosides have been considered as an effective combination against gram-positive and gram-negative microorganisms (12). However, some recent studies suggest a lack of evidence of superior efficacy of this combination to their individual use (monotherapy) and a higher incidence of adverse effects (13,14).

Antibiotic combinations are used when polymicrobial etiology is suspected or as an empirical treatment of infections that are caused by bacteria resistant to multiple antibiotics. Another indication for combined antimicrobial therapies is to prevent the emergence of resistant mutant microbial strains because there are higher chances that at least one of the pharmaceutical agents would be effective (1).

Patient-related factors that should be considered when selecting antimicrobial therapy are hepatic and renal function, age, genetic susceptibility, allergies, pregnancy, lactation, and prior antibiotic use.

In patients with compromised hepatic and renal function, the risk of accumulation and toxicity should be evaluated and, if necessary, the antimicrobial dose should be reduced (15). The dose must be carefully calculated according to their weight and kidney function in pediatric and geriatric patients. Furthermore, some drugs, such as tetracyclines, should be avoided in young children due to their accumulation in bone and teeth (16). Genetic variations and enzyme deficiencies should be considered when the risk of hemolysis, organ toxicity, hypersensitivity reaction, or other adverse effects is high (1,17). Antimicrobial therapy during pregnancy and lactation should be carefully evaluated to reduce the risk for both organisms. This includes selecting agents that do not pass the placental barrier, nor are excreted through the breast milk, and do not hide potential risks for baby development. Regarding the mother, the increase in plasma volume and renal blood flow can lead to more rapid clearance and lower drug serum levels (18). However, there is not enough evidence to support the increase in the doses in these patients (1). History of drug allergies should be carefully obtained and analyzed, and allergy tests should be conducted. It has been reported that only 10–30% of patients reporting penicillin allergy had positive allergy test results (19,20). When the drug of choice cannot be used due to a suspected allergy, allergy testing must be considered. A recent history (in the last three months) of antibiotic use can suggest resistant pathogens (1).

The route of administration (oral versus intravenous) depends on various aspects, such as the severity of the infection, gastrointestinal function, absorption, bioavailability, targeted serum levels, etc. (1).

The pharmacodynamic characteristics of antimicrobial drugs should also be considered, especially their activity which can be either time-dependent or concentration-dependent (21). Drugs with time-dependent ( $\beta$ -lactams, macrolides, clindamycin) killing require continuous infusion or frequent dosing, while those with concentration-dependent (aminoglycosides, fluoroquinolones, metronidazole) killing rely on peak serum concentrations. The efficacy of antimicrobial agents is based on their ability to reach a concentration equal to or higher than the MIC at

the site of infection. This is another key aspect of drug selection (1).

Along with the principles of antimicrobial treatment, clinicians should always evaluate the risk of adverse effects, dysbiosis, and AMR.

In 2019 WHO defined AMR as one of the most serious threats to public health (8). In 2022. The European Union states that it is among the three most serious threats with leading priority, which is the cause of the death of over 35 thousand people in the EU and over 1.2 million people worldwide every year (22). One possible reason for antibiotic overprescription is the routine antibiotic prophylaxis for surgical and other invasive procedures. Antibiotic prophylaxis has been excessively used to reduce the incidence of surgical site infections, prosthetic joint infections, and infectious endocarditis. However, recent guidelines have rejected this wrong practice (23–26). Antibiotic prescription should be based on the benefit-risk ratio. Some common mistakes when using antibiotics are: using inappropriate agents—against non-susceptible microorganisms; prescribing subtherapeutic doses for too long or a too short period of time; repeated use of the same antibiotic; risk of drug antagonism in incorrect antibiotic combinations, etc. (27–30). Therefore, global trends are aimed at developing strategies and a strict antibiotic policy to ensure antibiotic use only in cases with a high risk of severe infectious complications (31–33).

## CONCLUSION

Antimicrobial therapy should be based on selecting appropriate pharmaceutical agents and doses, route of administration, timing, and duration of the treatment. Numerous etiological and patient-related factors should be considered during the treatment. The growing risk of AMR requires more cautious behavior and strict following of the recommendations for good medical practice.

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