

Mechanisms of Action by Antimicrobial Agents: A Review

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1 | INTRODUCTION

The explosive growth in the use of antimicrobial therapy has provided a degree of control on microbial-related diseases in humans. However, microbial resistance to antibiotics also developed over time, resulting in an arms-race for developing newer agents against these more resistant strains. As a result, practicing clinicians have an obligation to remain informed on modern antimicrobial agents and to understand their core mechanisms of action. Bacteria and fungi differ in cellular composition, but the levels at which these microbes can be altered are similar: protein synthesis, nucleic acid syn-

ABSTRACT

Microorganisms and their associated conditions comprise some of the world's leading causes of death and have the potential to cause a significant effect on human activities during pandemic states. Despite such significance in the healthcare field, attention and funding directed towards microbiological research lags behind those given to cancer and cardiovascular disease. In the current SARS-CoV-2 pandemic, the need of healthcare providers to remain knowledgeable on antimicrobial therapy for their patients is greater than ever before. The scope of this review is to provide clinicians a semi-comprehensive, up-to-date understanding of the mechanisms of action among antimicrobial agents as well as key distinctions in clinical manifestations of pathogens.



KEYWORDS

Antimicrobial Activity, Mechanism of Action, Antiviral, Antifungal, Antibiotic

thesis, cell wall, and cell membrane. Viruses, on the other hand, are different structurally as they do not contain a cell membrane or cell wall. (1) The aim of this review is to provide a categorical overview of antimicrobial agent mechanisms and brief clinical manifestations.

2 | METHODS

An electronic database search was performed on MEDLINE (PubMed) using the following criteria: ("antimicrobial agents" [All Fields]) OR ("penicillin" [All Fields]) OR ("sulfonamide" [All Fields]) OR ("protein synthesis

antibacterial "[All Fields]) OR ("antifungal" [All Fields]) OR ("antiviral"[All Fields]) AND "access"[All Fields] AND "outcomes"[All Fields]). The results were narrowed down to 810 publications after filtering for free, full-text, and 88 publications were selected by the reviewers (SPS and AQ) for analysis. Afterwards, the reviewers excluded 18 duplicate publications, resulting in 70 publications for the final analysis. Additionally, two medical textbooks were used to yield relevant clinical information for medical students. (1, 63)

3 | ANTIBACTERIAL AGENTS

3.1 | Agents Acting Through Cell Wall Synthesis

While the organic synthesis and structure of the cell wall is different between bacteria and fungi, its presence helps limit changes in the internal osmotic pressure of both microbes. (1,2) Since the cell wall is not present in mammalian cells, this structure is a key antimicrobial target that minimizes impact on normal host tissue. (1)

3.1.1 | Beta-Lactam Containing Antimicrobials

Penicillin is a group of antimicrobials that resembles a structural analogue of D-alanyl-D-alanine in most cases. (2) This analogue competes for the D-alanyl-D-alanine transpeptidase, also known as the penicillin-binding protein, which joins layers of peptidoglycan on the cell wall. By inactivating peptidoglycan synthesis, penicillin creates higher internal osmotic pressure that leads to cell lysis. (2) Additionally, penicillin is a β -lactam drug because it contains an eponymous β -lactam ring essential for its function. When the β -lactam ring is destroyed, penicillin loses its analogous quality and no longer competes for transpeptidase. (4) Additionally, patients who are allergic to penicillin may resort to using alternative β -lactam drugs such as cephalosporins and carbapenems. (3) This group of molecules are structurally different from penicillin but are functionally similar and have a broad-range spectrum of bacterial coverage. (1-7) Bac-

terial resistance to β -lactam-containing agents develops during endogenous production of penicillinases/ β -lactamases by bacterial strains. To protect the β -lactam ring from degradation by these penicillinases, a large molecular side chain structure may be added. (2) This addition led to the creation of penicillinase-resistant penicillin (e.g. dicloxacillin, nafcillin, oxacillin). They have a smaller spectrum of activity, with targeted efficacy against *Staphylococcus aureus*. (1) Monobactams (e.g. aztreonam) comprise another β -lactam drug class that affect transpeptidation and are primarily used against aerobic Gram negative bacteria due to their molecular structure. (2-6)

3.1.2 | Vancomycin

While β -lactam drugs specifically target the transpeptidase, preceding enzymatic steps in peptidoglycan synthesis can also serve as antibacterial targets. For example, vancomycin binds directly to D-alanyl-D-alanine transpeptidase to inhibit cross-linking. (63) Vancomycin thus prevents peptidoglycan synthesis without being susceptible to β -lactamases. (1) Vancomycin is clinically used against methicillin-resistant *Staphylococcus aureus* (MRSA). Noteworthy side effects of vancomycin include nephrotoxicity, ototoxicity, and thrombophlebitis (similar effects are also found with aminoglycosides). (1) This review search yielded a case study of a patient who presented with "red man syndrome" due to vancomycin's ability to directly bind to mast cells causing them to release histamine, promoting vasodilation. (69)

3.1.3 | Bacitracin and Cycloserine

Bacitracin is an antibacterial agent that inhibits transport of peptidoglycan subunits from the cytoplasm to the cell wall by inactivating its phospholipid carrier. (7) In contrast, cycloserine inhibits synthesis of D-alanyl-D-alanine inside the cell. (7) Comparatively, the literature on cycloserine was scarce compared to other agents in this review, which could also imply that cycloserine is used less often in clinical settings than other agents.

3.2 | Agents Acting Through Microbial Protein Synthesis

3.2.1 | Aminoglycosides

Aminoglycosides are a broad-spectrum bactericidal class of antibiotics that can be semi-synthetic or naturally derived from Gram positive actinomycetes. (13) They exert their antibacterial effects by inhibiting the prokaryotic ribosomal initiation complex, which results in misreading of messenger RNA (mRNA). (1) Oxygen-dependent active electron transport is required for aminoglycoside uptake into cells, explaining their lack of activity against anaerobic bacteria. (13) Streptomycin is an aminoglycoside that irreversibly binds to the A-site 30S ribosomal subunit of the initiation complex in bacteria. (1,15) Furthermore, streptomycin can be nephrotoxic as well as ototoxic due to degeneration of sensory cells in the basal cochlea. (15,16) While streptomycin is no longer used as widely in Canada or the United States anymore, it holds historical importance because it was the first aminoglycosides discovered for clinical use, specifically against tuberculosis, bubonic plague, and brucellosis. (1) Other aminoglycosides include gentamicin (used against various Gram-negative rods such as *Pseudomonas aeruginosa*), amikacin (used against gentamicin-resistant organisms), and neomycin (used against various enteric gram negative rods). (13) Aminoglycosides usually are not given orally as they are poorly absorbed in the GI tract. (1,13) However, oral neomycin is given in preoperative bowel preparation. (1)

3.2.2 | Tetracyclines

Tetracyclines are bacteriostatic antibiotics that, like aminoglycosides, inhibit microbial protein synthesis by binding to the 30S ribosomal subunit. (63) However, rather than binding irreversibly to the A-site 30S ribosomal subunit of the bacterial initiation complex, tetracyclines reversibly inhibit the binding of transfer RNA (tRNA) to the acceptor site, hindering polypeptide growth. Tetracyclines also chelate calcium and iron, and hence should not be taken simultaneously with supplement forms of calcium and iron to avoid micronutri-

ent deficiencies. In addition, tetracycline is contraindicated in infants and in pregnancy due to tooth discoloration through calcium-chelation. (17) A newer class of antibiotics called tigecyclines are structurally similar to tetracyclines and also bind to the 30s ribosomal subunit. (1) Clinically, tigecycline are used to treat complicated intra-abdominal infections and skin/soft tissue infections, with notably activity against MRSA. (59)

3.2.3 | Chloramphenicol

Chloramphenicol is a broad-spectrum antibiotic that blocks peptidyltransferase at the 50S ribosome subunit to prevent protein synthesis. This class of antimicrobials is bacteriostatic against many bacteria responsible for ocular infections. The literature notes bactericidal activity against the meningitis-causing microbes *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae*. (63) Chloramphenicol toxicity comes in two forms: 1) a predictable, reversible, dose-dependent bone marrow suppression that can start soon after administration; 2) an unpredictable, rare, and disastrous irreversible agranulocytosis, which generally occurs during prolonged therapy. (18) Metabolically, chloramphenicol is detoxified through UDP-glucuronyl transferase. (1,18) Toxic chloramphenicol serum concentration may result in gray-colored skin and cyanosis in infants, which has been documented as infantile “gray-baby” syndrome. (71)

3.2.4 | Macrolides and Clindamycin

Macrolides interact through the 50S ribosome subunit of bacteria via blocking translocation of tRNA. (63) Azithromycin is a macrolide used to treat respiratory tract infections and *Chlamydia*-induced genital tract infections. (18) Clarithromycin has a similar spectrum and treats *Helicobacter* infections such as peptic ulcer disease. Side-effects include arrhythmia from QT-prolongation and cholestatic hepatitis. (63) Both clarithromycin and erythromycin were shown in a study to inhibit cytochrome P-450. (19)

Clindamycin also inhibits translocation of tRNA on

the 50S ribosome subunit of bacteria. (1,63) It is used to treat anaerobic infections above the diaphragm such as aspiration pneumonia and lung abscesses. (1,19) A major adverse effect of clindamycin is the overgrowth of a drug-resistant strain of *Clostridium difficile* in the gastrointestinal tract, which can produce an exotoxin leading to pseudomembranous colitis. (19)

3.2.5 | Oxazolidinones

Oxazolidinones inhibit the formation of the initiation complex on the 50s ribosomal subunit. These agents are particularly useful against MRSA, vancomycin-resistant *Enterococci*, and penicillin-resistant *Streptococcus pneumoniae*. (21,63) Adverse effects include serotonin syndrome and tyramine-induced hypertensive crisis, since some oxazolidinones such as linezolid are monoamine oxidase inhibitors. (21)

3.3 | Agents Acting Through Nucleic Acid Synthesis

3.3.1 | Sulfonamides and Trimethoprim

Sulfonamides competitively inhibit p-aminobenzoic acid (PABA), an early precursor of tetrahydrofolic acid, which is required for nucleic acid synthesis of all nitrogenous bases except cytosine. (22) By inhibiting PABA, sulfonamides render the dihydropteroate synthase inactive. (1,22,63) Clinically, sulfonamides are used to treat urinary tract infections caused by *Escherichia coli* as well as middle ear infections caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*. (22) Moreover, it is critical to understand that while nucleic acids are present in both prokaryotes and eukaryotes, mammalian cells do not have PABA-containing precursor enzymes and instead rely on exogenous folic acid to meet their metabolic requirements for nucleic acid synthesis (23), which in theory can limit sulfonamides targeting of mammalian cells. Sulfonamides are commonly used in combination with trimethoprim. (23) Trimethoprim similarly inhibits the production of tetrahydrofolic acid, but its mechanism involves the inhibition of a later enzyme in

the pathway, dihydrofolate reductase. (1,63) Thus, sulfonamide and trimethoprim act synergistically. However, as trimethoprim inhibits folic acid synthesis, bone marrow suppression may result, leading to potential megaloblastic anemia. (22)

3.3.2 | Fluoroquinolones

Unlike sulfonamides and trimethoprim, which are independent bacteriostatic agents, fluoroquinolones are bactericidal drugs that inhibit DNA gyrase and DNA topoisomerase in bacteria. (26) Fluoroquinolones (e.g. ciprofloxacin, levofloxacin, etc.) can be used to treat urinary tract infections and lower respiratory tract infections caused by Gram negative rods. (1) Side effects of fluoroquinolones include tendonitis and/or tendon rupture in elderly patients. (63) Fluoroquinolones have been contraindicated in children and pregnant women due to potential interference with bone growth, but this has only been reported in animal models. (26-27)

3.3.3 | Rifamycin

Rifamycins selectively bind to the β subunit of bacterial RNA polymerase, rendering it inactive for mRNA synthesis. (1) Rifampin is specifically useful in the treatment and prophylaxis of *Mycobacterium tuberculosis*-caused tuberculosis and meningitis, respectively. (31,63) It also aids in the treatment of leprosy by attenuating antimicrobial resistance to dapson. (31) Patients on rifampin may have harmless reddish orange urine (1) due to the drug's color being distilled by body fluids. Rifampin may also result in hepatotoxicity as it induces cytochrome P-450 enzymes; thus it is not recommended for HIV patients. (1) Rifabutin is a rifampin derivative that can be used by HIV patients as it induces cytochrome P-450 enzymes to a lesser degree than rifampin. (30,31)

3.4 | Agents That Alter Cell Membranes

3.4.1 | Polymyxin and Daptomycin

Polymyxins such as Polymyxin E proteins disrupt the charge of phospholipids in the bacterial cell membrane. (32) They are useful against many Gram-negative rods and carbapenemase-producing *Enterobacteriaceae*. (63) Daptomycin similarly disrupts the cell membranes of gram positive cocci and MRSA through depolarization, but is not effective in the lung due to pulmonary surfactant interfering with its mechanism of action. (32)

4 | ANTIFUNGAL AGENTS

The fungal cell wall is composed of a solubilized chitin- β -(1,3)-glucan linked by a β -(1,6)-glucan to mannoproteins on the outer surface of the fungal cell wall. (10) β -glucan is synthesized by a multi-subunit enzyme, 1,3- β -glucan synthase. (11) Previous literature on this enzyme shows that its inhibition results in physiological cell cycle arrest and hence has become a key target in antifungal therapy through the echinocandin lipopeptide class of antifungal therapy. (10-11)

4.1 | Agents that Alter the Cell Wall

Caspofungin is a part of the echinocandins, a lipopeptide drug class that non-competitively inhibits 1,3- β -glucan synthase. It is mainly used against systemic yeast infections, such as disseminated candidiasis and invasive aspergillosis. (11) However, caspofungin has been shown to be ineffective against *Cryptococcus* or Mucor-induced infections at normal doses. (12) Additionally, another lipopeptide drug, micafungin, has been used for prophylaxis in patients undergoing hematopoietic stem cell transplantation. (70) Anidulafungin is another semisynthetic echinocandin used against invasive esophageal candidiasis in clinical use. (12) *Cryptococcus* is not susceptible to any of the three semisynthetic echinocandins, but the mechanism of this resistance is not well understood. (1, 11)

4.2 | Agents that Alter the Cell Membrane

Amphotericin B is an antifungal that alters the cell membrane by binding to ergosterol - a compound exclusive to fungi. (1) This results in the formation of ion channels in the fungal cell membrane leading to depolarization of the cell membrane and subsequent cell death. (33) Additionally, amphotericin B is associated with nephrotoxicity and arrhythmia, which causes its use by clinicians to be reserved for salvage therapy. Nystatin is a topical antifungal agent that functions similarly to amphotericin and is used for topical *Candida* infections. (1) Azoles are another class of antifungal cell membrane agents. They work by directly inhibiting ergosterol synthesis. (34) Terbinafine inhibits a squalene epoxidase in ergosterol synthesis and is used in finger and nail fungal infections. (33,63)

4.3 | Agents that Alter the Nucleotide and Protein Synthesis

The scope of fungal nucleic acid inhibitors is smaller. The primary antifungal agent is flucytosine, a nucleoside analogue that can inhibit a thymidine precursor enzyme, resulting in inactive DNA synthesis. (28,29) Griseofulvin and pentamidine are antifungal agents that alter microtubules and DNA synthesis, respectively. (63) Pentamidine is used for treatment and prophylaxis against *Pneumocystis jiroveci*. (35) Griseofulvin, like terbinafine, is useful in fungal infections of the nailbed. (35,36)

5 | ANTIVIRAL AGENTS

Unlike bacteria and fungi, viruses are acellular structures containing their own set of DNA or RNA and a limited variety of proteins necessary for nucleic acid replication and structural attachment/maintenance. (1,63)

5.1 | Herpesvirus

The primary herpesviruses of this review are Herpes Simplex Virus type 1 & 2 (HSV-1 & HSV-2), cy-

tomegalovirus (CMV), Epstein-Barr virus (EBV), and Varicella-Zoster virus (VZV). (58) While HSV-1 is commonly associated with oral cold sores, HSV-2 is usually associated with genital blisters or sores generally below the waist. (42) Patients acutely infected with VZV initially present with febrile symptoms and can develop varicella, while post-latency VZV re-activation commonly causes a dermatomal rash known as shingles. VZV is also associated with vesicular rashes, neuritis, and encephalitis. (1,42) Regarding CMV infection, congenital manifestations such as intracranial calcifications, hydrocephalus, and retinitis are present both with and without symptoms. (42,63) Symptoms in patients infected with CMV include mononucleosis (more common post-neonatally), rash, and malaise. (1) EBV and CMV infections are similar in that both infected children and adults present with mononucleosis-related glandular fever. (1,58)

Inhibitors of the herpesviruses can be separated into nucleoside inhibitors and non-nucleoside inhibitors. Acyclovir, ganciclovir, and trifluridine are nucleoside inhibitor analogues that vary in function. Acyclovir is a nucleoside analogue that is preferentially activated by a virus-encoded thymidine kinase primarily found in HSV. (1) Upon phosphorylation of acyclovir, a cellular by-product, acyclovir triphosphate, inhibits the viral DNA polymerase and subsequent nucleic acid synthesis. Clinically, acyclovir is used in the treatment of genital herpes and is used as a prophylactic agent in patients who are immunocompromised or elderly. (73) Despite its efficacy against active HSV, acyclovir has minimal effect on latent HSV and VZV. (58) Ganciclovir is structurally similar to acyclovir, but is preferentially activated by a CMV-encoded phosphokinase to inhibit viral nucleic acid synthesis. (58,63) Cidofovir is another nucleoside analogue that is approved to treat CMV-induced retinitis. (63) In contrast, the non-nucleoside inhibitor of HSV is foscarnet, a pyrophosphate analogue that directly binds to DNA polymerase during pyrophosphate cleavage. This agent is clinically useful against acyclovir-resistant active HSV and CMV infections. (37,38)

5.2 | Hepatitis B and C

There are multiple types of hepatitis viruses (A, B, C, D, E), but this review will focus on Hepatitis B and C (HBV & HCV) as they are more likely to cause chronic infection and can also progress into hepatocellular carcinoma (1,52-53); however, it is imperative to know that malaise, jaundice and transaminitis are common manifestations in acute viral hepatitis of any cause. The primary agents acting against chronic HBV infections inhibit viral DNA polymerase, but each of these primary drugs are structurally different analogues, such as entecavir (guanosine analog), adefovir (adenosine monophosphate analogue), and telbivudine (thymidine analogue). The prominent HCV antiviral agents can be separated into RNA polymerase inhibitors (dasabuvir, sofosbuvir & simeprevir), nonstructural protein 5a (NS5A) inhibitors (ledipasvir, ombitasvir), and nonstructural protein 5B (NS5B) inhibitors. Their mechanisms of action are beyond the scope of this review. (42-44) Recombinant alpha interferon can also be used against hepatitis B and C infections, but this treatment has fallen out of favor in the past decade due to an unfavorable side-effect profile. (72)

5.3 | Influenza B and C

All case studies derived for this review noted the specific strains of Influenza A and B during seasonal epidemics of the flu. Oseltamivir is an oral antiviral medication used to prevent influenza A and B outbreaks. (39,54) Once activated, this pro-drug selectively binds to neuraminidase, an enzyme found on the outer surface of all influenza viruses, to prevent viral release. (1) Other analogues include zanamivir and peramivir. (1,39,54) Baloxavir is a selective inhibitor of influenza cap-dependent endonuclease, and has been shown in clinical trials to reduce viral load more efficiently than oseltamivir. (74). It is currently clinically approved for its medical use in Influenza A infections in the United States. (54)

5.4 | Human Immunodeficiency Virus

Human Immunodeficiency Virus (HIV) is characterized by a unique diploid set of viral RNA. The virus infects and destroys CD4+ T helper cells, thereby weakening the immune system. (1,63) Patients often initially present with a febrile illness resembling mononucleosis, marking the acute phase of the viral infection. (1) The virus then enters the latency phase where it seeds and replicates within latent HIV reservoirs in the body.(1,63) This period can take months to years while the patient is asymptomatic. (1) Eventually, CD4+ serum count decreases causing moderate immunocompromise followed by the Acquired Immunodeficiency Syndrome (AIDS) phase of the infection, characterized by severe opportunistic infections. (5,57)

To delay this decline in immune function, multiple agents against HIV are given in combination. (57) The first two major classes of HIV drugs are nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). (57) NRTIs include Abacavir, Didanosine, Emtricitabine, Lamivudine, Stavudine, Tenofovir, and Zidovudine. (63) While each NTRI vary slightly in structure, they all competitively bind to the HIV reverse transcriptase active site to inhibit viral DNA synthesis, causing chain termination. (1) NNRTIs include Delavirdine, Efavirenz, Etravirine, Nevirapine, and Rilpivirine, all of which inhibit viral DNA synthesis through allosteric inhibition of reverse transcriptase activity. (1,57) Other classes of HIV drugs include protease inhibitors (i.e. lopinavir, ritonavir) and integrase inhibitors (i.e. raltegravir, dolutegravir), which work on their namesake enzymes involved in the systemic growth of the virus. (1)

6 | DISCUSSION

The core target mechanisms of antimicrobial structure and macromolecule synthesis that were discussed remain classic starting points for the study of novel therapeutic techniques. This review analyzed over 70 academic pieces of literature to provide the most current understanding for healthcare professionals. While most

of the antimicrobial agents discussed are likely to be seen in clinical practice, this review does not encompass all agents approved for treatment, nor does it provide new data on the efficacy of these agents. This review suggests that future systematic reviews are needed to provide directions for research on antimicrobial agent mechanisms. Additionally, the timing of this paper coinciding with the ongoing worldwide COVID19 pandemic serves a key role in providing a semi-comprehensive, up-to-date understanding of the mechanisms of action of antimicrobial agents in times where many entities are exploring variations and manipulations of these agent mechanisms. (63, 66) For example, recent literature suggests that members of the aforementioned fluoroquinolone family of nucleic acid synthesis inhibitors can be used as a form of therapy against COVID-19. The basic mechanisms of action are therefore more pertinent than ever before and open an avenue for discussion of the uses of combination and crossover therapies by these agents.

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