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MOLECULAR BASIS OF ANTIBIOTIC RESISTANCE, GENETIC MECHANISM AND THERAPEUTIC STRATEGIES

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ABSTRACT

Antibiotic resistance has become a global health crisis, driven by transferable resistance genes and diverse molecular mechanisms. Bacteria evade antibiotics through three core strategies: preventing drug access, altering or protecting targets, and directly inactivating drugs (e.g., via β-lactamases). Despite the clinical success of β-lactams–over 40 variants widely used–bacterial enzymes now threaten their utility. Even β-lactamase inhibitors are losing effectiveness as resistant mutants emerge.

Genetic mechanisms include mutations and horizontal gene transfer. Biochemically, resistance arises through drug inactivation (β-lactamases, acetylases, phosphorylases), target modification (altered penicillin-binding proteins), permeability changes, and active efflux pumps. Clinically significant examples include enterococci (intrinsic and acquired resistance to multiple drug classes) and staphylococci (altered PBPs and β-lactamase expression). The transfer of glycopeptide resistance from enterococci to staphylococci is particularly concerning.

Antimicrobial resistance (AMR) emerges from overuse in human medicine, veterinary practice, and agriculture, creating selection pressure. Multidrug resistance (MDR) involves genomic duplication, enzymatic modification, target alteration, membrane modulation, and efflux pumps, leading to treatment failures. New therapeutic directions include antivirulent therapy, antimicrobial peptides, phage therapy, vaccines, and nanoparticles.

Combating AMR requires antimicrobial susceptibility testing, rapid diagnostics, timely clinical response, and novel pharmacodynamic approaches. The genetic plasticity of bacterial pathogens–through mutations and gene acquisition–has enabled resistance to nearly all clinical antibiotics. Understanding biochemical and genetic fundamentals is essential to reduce resistance transmission and develop effective therapies against multidrug-resistant organisms. Without urgent action, we face an era where common bacterial infections may become untreatable.

Keywords: *antimicrobial agent; drug; antibacterial drug; bacteria; antibiotic resistance; efflux; multidrug efflux*

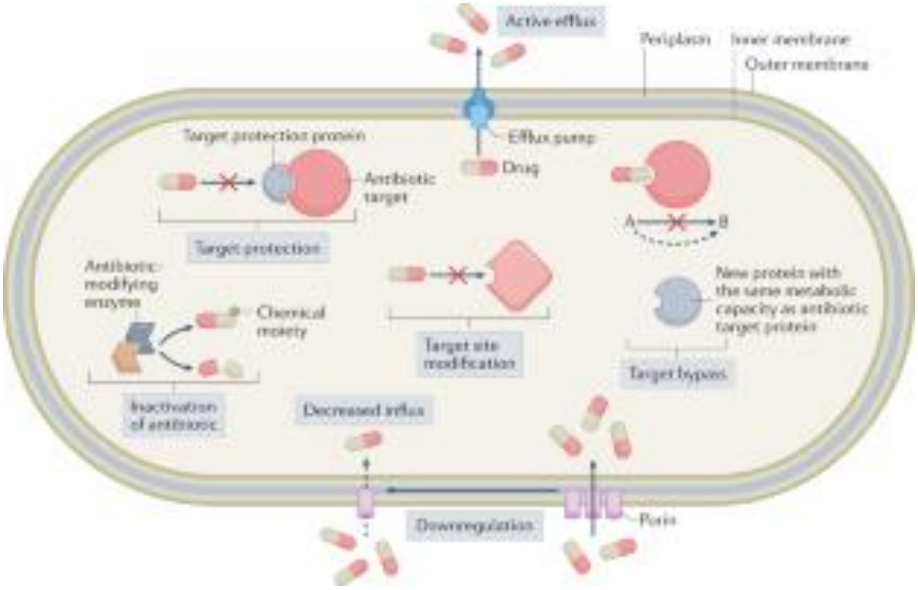
INTRODUCTION

Causative agent bacteria are an important health issue across the world. The use of antimicrobial agents is indicated in the treatment of bacterial infections. Bacteria can be inherently resistant to antibacterial agents, or can develop resistance through mutation or acquisition of resistance determinants. The antimicrobial agents produce a

selective pressure on the bacteria within a population such that the less susceptible, or resistant, bacteria are selected by the antimicrobial agent, resulting in a scenario where the resistant bacterial variant appears dominant under such selective pressure [1]. Moreover, the resistance of individual antimicrobial agent is frequently selected leading to bacterial variants that carry transferable multidrug resistance determinants [2].

Until the discovery of third distinct Cefotaxime degrading enzyme CTX-M type in E. coli in 1990, TEM and SHV were the predominant ESBLs, and today there are over 40 different CTX-M ESBLs types [3]. ESBLs hydrolyze a diverse variety of cephalosporins including the oxyimino group of cephalosporins like ceftriaxone, ceftazidime and cefotaxime and the monobactam drugs like aztreonam, but not cephamycins and carbapenems [4].

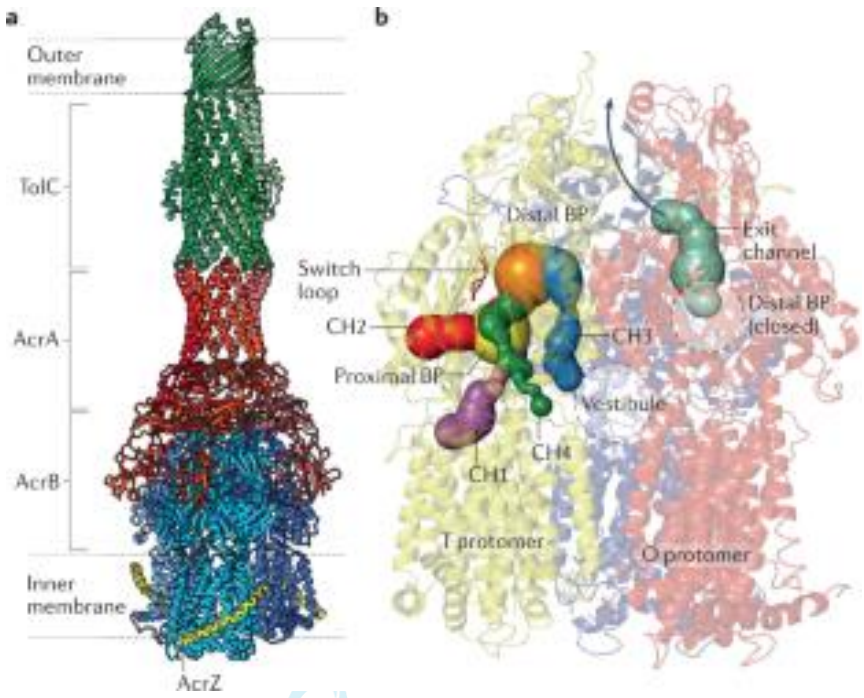
Overview of the molecular mechanisms of antibiotic resistance.



Moreover, ESBLs based on OXA-type 8 -lactamase provide resistance to cloxacillin and oxacillin antibiotics and are called OXA-type ESBLs. OXA types are not clavulanate and tazobactam resistant as compared to TEM and SHV ESBLs. At present, over 200 different ESBL types have been identified in different parts of the world and these have developed out of TEM, SHV and CTX-M types through point mutations [5].

The second way of antibiotic inactivation is through enzyme-mediated structural modification of the drug through transfer of a functional group including acyl, ribosyl, phosphoryl or thiol group. The modification of the antibiotic is irreversible and the altered antibiotic cannot bind to the target because of the subsequent alteration of the structure. Aminoglycosides, fosfomycin, macrolides, lincomycin and chloramphenicol are the antibiotics that are susceptible to this bacterial mechanism. An example is the development of acetyl transferases in bacteria that inactivate chloramphenicol, tetracycline-metabolizing enzymes that have little characterization, and beta-lactamases that inactivate betalactams such as penicillin [6].

Structure and entry channels of RND efflux systems.



A variety of drug-resistant microbes have been identified by the World Health Organization WHO and scientific literature. These include vancomycin-resistant Enterococcus VRE, imipenem-resistant Acinetobacter baumannii, methicillin-resistant Staphylococcus aureus MRSA, cephalosporin-resistant Escherichia coli, clarithromycin-resistant Helicobacter pylori, fluoroquinolone-resistant Campylobacter spp., fluoroquinolone-resistant Salmonella, cephalosporin-resistant and fluoroquinolone-resistant Neisseria gonorrhoeae, penicillin-non-susceptible Streptococcus pneumoniae, ampicillin-resistant Haemophilus influenzae, fluoroquinolone-resistant Shigella spp., and several other resistant Gram-negative pathogens [4,5]. These organisms have turned out to be more challenging to treat posing a severe and chronic public health issue [5]. Most of the strains are now resistant not to a single antimicrobial agent but to a number of drugs and its widespread spread is prevalent in the community [6]. Colistin and carbapenem resistance has also been documented, which is particularly worrying since they are regarded as the last-line agents against Gram-negative bacteria GNB [7].

Drug inactivation mechanisms

The bacteria have developed various strategies of making antimicrobials inactive including enzymatic hydrolysis of antibiotics, group transfer and redox process [8]. The classical example of such a mechanism is the synthesis of βlactamases which cleave the 2-lactam ring of penicillins.

The situation related to the management of AMR is ambiguous and secretive. Newer classes of antimicrobial drugs with multiple mechanisms need to be explored to develop novel ways to revolutionize the resistance and to turn up alternatives to antimicrobials that would potentially help to curb AMR and eventually noxious infections. The main kingpin of this article is to demonstrate the use of alternative therapeutics of antibiotics and cutting-edge methodologies to bridge the gap between early discovered drugs and clinical development, which might lead to diminished AMR. The need of the hour is to explore new target techniques and synergetic policies both at the national and international level in order to pass AMR.AMR is the ultimate challenge in management of infectious diseases, a serious threat to public health on an international scale.

LITERATURE REVIEW

The resistance to antibiotics has become one of the most urgent worldwide health issues of the 21 st century. Excessive and inappropriate use of antibiotics in human medicine, agriculture and veterinary practice exert intense artificial selection pressure on bacteria, which leads to their rapid evolution and dissemination of resistant strains. In microbiology, genomics and publication health literature all emphasize that antibiotic resistance is not a solitary fact, but a group of molecular adaptations, genetic swamping and ecological forces that are all united to undermine the efficacy of current treatments. The review is a synthesis of the results of the earlier research articles, systematic reviews, and recent developments that offer a broad insight into the molecular basis of resistance, genetic processes that are involved, and treatment strategies that have been developed to overcome resistance.

The ever increasing number of multidrug-resistant microorganism pathogens has become a great and global public health threat, Daniela S. Pontes 01 Jan 2018. The mechanisms of action of the antibiotics and the mechanisms of resistance are closely related, yet the understanding of the biochemical and molecular action of such drugs is not an easy task. The environment, and genetic settings both play a role in changing phenotypic resistance natural evolution of bacteria, and complicate management of the development and effects of antibiotic resistance. Under such circumstances, comprehension of how bacteria develop and/or acquire antibiotic resistance genes ARG has a critical role in developing propositions to fight against these superbugs, and to search for new drugs.[9]

Jose M Munita 2016 Emergence of resistance among the most significant bacterial pathogens can be defined as a significant threat to human health on a global scale. Not only have multidrug-resistant organisms developed in the hospital setting but they are currently frequently found in the community setting, potentially indicating the existence of reservoirs of antibiotic-resistant bacteria outside the hospital. The bacterial response to the antibiotic "attack" is the prime example of bacterial adaptation and the pinnacle of evolution. Survival of the fittest is an outcome of a massive genetic plasticity of bacterial pathogens that induce certain responses which lead to mutational adaptations, acquisition of genetic material or a change in gene expression leading to resistance to practically all currently used antibiotics in clinical practice. Thus, a biochemical and genetic explanation of resistance would be of utmost importance to develop strategies to reduce the appearance and dissemination of resistance and to develop new approaches to treat multidrug-resistant organisms. The chapter will further elaborate on the key mechanisms of antibiotic resistance that we come across in clinical practice with specific examples in the relevant bacterial pathogens. [10]

Natalia Dekhnich 2, Igor Khatkov 2023 Helicobacter pylori is one of the most common cause of human infections. All infected patients have chronic active gastritis that may result in peptic ulcer, atrophic gastritis, gastric cancer and gastric MALT-lymphoma. The prevalence of H. pylori infection in the population has regional characteristics and can reach 80%. The constantly rising resistance of H. pylori to antibiotics is one of the primary reasons of failure in treatment, and a key issue. The VI Maastricht Consensus suggests two approaches to the selection of eradication therapy: individualized depending on the assessment of sensitivity to antibacterial agents phenotypic or molecular genetic approach before assigning them, and empirical, which considers data on local H. pylori resistance to clarithromycin and surveillance schemes of effectiveness in the area. Thus, the establishment of the H. pylori resistance to antibiotics, in particular, clarithromycin, before selecting the therapeutic plan is exceptionally crucial to the introduction of such treatment plans. [11]

Andrew T Nishimoto 1, Cheshta Sharma 1, P David Rogers 1 2020 Candida albicans is an opportunistic yeast and the major human fungal pathogen in the USA, as well as in many other regions of the world.d. C. albicans infections may cause mild, superficial mucosal and dermatological infections, as well as fatal blood and vital organ infections. The azole antifungals remain an important mainstay treatment of candidiasis and therefore the investigation and understanding of the evolution, frequency and

mechanisms of azole resistance are vital to improving treatment strategies against this organism. The organism C. albicans and the genetic variations and bases of the existing known resistance mechanisms to the azole antifungal class including up-regulation of efflux pumps, modulation of the expression and amino acid composition of the azole target Erg11 and alteration of the normal pathways of sterol biosynthesis in the organism are reviewed. We also revise what is known of the activation of mutations in the zinc cluster transcription factor ZCF genes which regulate most of these resistance mechanisms, and overview azole import as a possible cause of azole resistance. Finally, the studies of azole resistance in C. albicans and its clinical implications are discussed. [12]

Osman Türkyılmaz 1, Cihan Darcan 2 2026 Due to the increasing antibiotic resistance profile, the efficacy of ampicillin – one of the main treatment options in clinical practice for many years – has markedly declined. The molecular mechanisms by which this antibiotic becomes less effective are important to comprehend in order to optimize the current treatment regimens and create new drugs with less resistance. This review studies the molecular basis of ampicillin resistance in a multilayered approach, offering a thorough analysis of how processes like production of 8-lactamases, changes in penicillin binding proteins, porin changes, activation of efflux pumps and combinations of the above mechanisms can contribute to ampicillin resistance according to the existing literature. Moreover, we also talk about the way that various mechanisms of resistance can be coordinated to form a coordinated resistance matrix. Lastly, we consider how these mechanistic considerations can be used to inform the creation of future therapeutic approaches to beat ampicillin resistance and how to determine the future therapeutic potential of multi-targeted therapies. [13]

Among the gram-positive bacteria, some of the more problematic drug-resistant pathogens today include methicillin-resistant Staphylococcus aureus, multidrug-resistant Streptococcus pneumoniae and vancomycin-resistant Enterococcus spp. and among the gram-negative bacteria, multidrug-resistant Acinetobacter ba The particular resistance issues that this review is concerned with are the resistance problems of P. aeruginosa and the complexity with which the major chromosomally encoded resistance mechanisms are controlled and coregulated to render P. aeruginosa one of our most serious therapeutic challenges.

MATERIAL AND METHODS

This study employed a literature-based analytical approach to investigate the molecular mechanisms, genetic basis, and therapeutic strategies of antibiotic resistance. The systematic review was conducted over four months at the Department of Medical Laboratory Technology, Superior University, Lahore. A non-probability purposive sampling technique was used to select 40–60 peer-reviewed articles published between 2020 and 2026, including systematic reviews, meta-analyses, and original research articles. Articles published before 2010, non-peer-reviewed content (blogs, editorials, opinion pieces), and duplicate or incomplete studies were excluded. Data were collected through structured searches of electronic databases including PubMed, Google Scholar, ScienceDirect, SpringerLink, Wiley Online Library, Nature, and Elsevier journals. As a secondary data study with no direct human or animal subjects, ethical considerations included proper citation to prevent plagiarism and adherence to the ethical standards of Superior University, Lahore. No statistical software was used, as this was a qualitative review.

Main Body:

This is especially typical in Gram-positive bacteria during conjugative transposon replication and transfer; a conjugative transposon that carries the vanA resistance gene is a part of such a transposon. In transduction, the resistance genes are adenovirally into bacterial phages bacterial viruses and subsequently discharged in a novel strain after the bacterial phage infects it. This process is probably quite important among S. aureus, which has barriers to the receipt of both conjugative transposons and incoming DNA. Transformation is a very important process particularly amongst S. pneumoniae, N. gonorrhoeae, and Neisseria

meningitidis. This is accomplished by taking up naked DNA through the cell wall which is in a competent state and integrating the newly acquired DNA into the established genome or plasmid. The acquired DNA sequences of penicillin-binding proteins which have been acquired by commensal streptococcal species probably in the naso-pharynx of patients infected with pneumococci confer penicillin resistance as observed in pneumococci, the genes being found to have a mosaic structure. [14]

Table: Molecular Basis of Antibiotic Resistance, Genetic Mechanisms, and Therapeutic Strategies

Aspect	Key Elements	Examples / Notes
Molecular Basis of Resistance	Enzyme production, target modification, efflux pumps, reduced permeability	β-lactamases (CTX-M), altered PBPs (*S. pneumoniae*), efflux systems
Genetic Mechanisms	Conjugation, transduction, transformation	*vanA* (transposons), phage-mediated transfer in *S. aureus*, DNA uptake in *Streptococcus pneumoniae*, *Neisseria* spp.
Genetic Adaptation	Mutation and recombination (mosaic genes)	Altered penicillin-binding proteins → β-lactam resistance
Transmission Pathways	Human–animal–environment cycle, faeco-oral spread	CTX-M *E. coli* (food chain), hospital/community circulation
Selective Pressure	Antibiotic misuse, agricultural use, biocides	Quaternary ammonium compounds selecting resistance
Therapeutic Strategies	Antibiotic stewardship, combination therapy, novel drug development	Control of MDR strains, need for new antimicrobials

We are now living in a microbiologically connected world where animal resistance genes can enter our bowel flora which can be excreted and through the sewerage system can be passed back into the land. We also have cycling of bacteria and hence resistance genes in hospitals and in the community of resistant strains by both contact and through other routes, such as the faeco-oral route. There is also selective pressure applied not only by the medical use of antibiotics, but also by the agricultural use of antibiotics, and there is even evidence that some compounds not thought of as having antimicrobial activity, such as quaternary ammonium compounds used in fabric conditioning, can select for antibiotic resistance genes Gaze et al., 2005. This interlinked network of cycles of transmission is illustrated in Examples of the movement of resistance genes either in humans to animals or in the reverse is illustrated: a cause of concern is the recent finding of CTX-M resistance genes in E. coli in chicken meat imported in to the UK where specific genotypes in human patients like CTX-M-2 in South America were detected in 50% of imported pre-prepared chicken breasts in the UK. [15]

There are also pressures to use antimicrobials both by the commercial exploitation and development of antimicrobials and by the humanitarian desire to treat infected humans and animals. We are living in the world where people and food, and other goods have a higher mobility which contributes to the increased possibility of the appearance of resistant clones of bacteria that can be developed in remote places. When the carriage of CTX-M beta-lactamase genes in faecal flora of the Chinese and Indian community is considered, it is estimated that this could be up to 10% and with a combined population of 2.5 billion people, this would mean that this would be the largest reservoir of antimicrobial resistance genes that can cause resistance to significant antibiotics used to treat Gram-negative infection Ensor et al Only with judicious use of antimicrobial drugs and the development of new and effective agents especially against multi-drug-resistant strains as a global initiative will the tide

of antibiotic resistance be held back. We should always be aware that in geological time we have only had effective antimicrobial therapy for infections for a fraction of a second, and it is important that we continue to have the facility to continue to treat serious bacterial infections. [16]

7.1: CONCLUSION(S)

Antimicrobial agents target cell wall synthesis, protein production, nucleic acid synthesis, and prokaryotic metabolic pathways. However, bacteria rapidly develop resistance to all drug classes through favorable mutations and horizontal gene transfer. Horizontal transfer occurs via three main mechanisms: conjugation, transduction, and transformation. In conjugation, Gram-negative bacteria transfer double-stranded circular DNA (plasmids) through a pilus. Conjugative plasmids can also capture chromosomal genes and mobilize non-transferable plasmids, bridging environmental resistance genes into clinically important bacteria. Most Gram-negative resistance genes reside on transposons, which replicate and transfer between plasmids and chromosomes. Integrons provide additional capture and expression of genes such as blaCTX-M. Conjugation is replicative, meaning the recipient gains a plasmid copy while the donor retains it. Conjugation also occurs in Gram-positive bacteria, often initiated by sex pheromones that induce cell clumping and DNA exchange.

7.2: RECOMMENDATION(S)

Based on the findings of this review, it is recommended that healthcare institutions increasingly integrate Next-Generation Sequencing (NGS) into clinical diagnostics to improve accuracy and support personalized medicine. Investment in training programs for laboratory personnel and clinicians is essential to enhance skills in molecular techniques and bioinformatics for effective interpretation of sequencing data. Strategies to reduce the cost of NGS should be explored to make this technology more accessible to a wider patient population. Furthermore, the development of standardized protocols and regulatory guidelines is crucial to ensure the consistency, quality, and reliability of NGS-based testing. Ethical considerations, including data privacy and management of incidental findings, must be addressed through clear policies.

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