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Adaptive Strategies of Human Pathogenic Bacteria- Antibiotic Resistance, Host Immune Manipulation and Microbial Persistence Mechanisms

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ABSTRACT

Human pathogenic bacteria employ diverse strategies to survive antibiotics and host defenses. These adaptations contribute to chronic infections, treatment failures, and increased morbidity and mortality. This review explores three primary bacterial survival strategies antibiotic resistance, modulation of host immune responses, and microbial persistence. Antibiotic resistance arises through multiple genetic and biochemical mechanisms, including target modification, enzymatic inactivation, efflux pump overexpression, and horizontal gene transfer. Beyond resistance, pathogens actively manipulate host immune responses to evade detection, modulate immune signaling, and enhance colonization and dissemination. Additionally, microbial persistence mechanisms such as biofilm formation, phenotypic heterogeneity, and the emergence of persister cells allow bacteria to withstand antimicrobial treatments and immune-mediated clearance without acquiring permanent genetic resistance. These processes are not isolated; rather, they interact and reinforce each other, creating a complex network of survival strategies. Understanding these interconnected mechanisms is essential for designing more effective therapeutic approaches. By integrating insights from molecular microbiology, immunology, and clinical research, this review aims to provide a comprehensive framework for understanding bacterial adaptability. Such an integrated perspective can help identify potential targets for future antimicrobial and immunomodulatory therapies, ultimately improving the management of infections caused by multidrug-resistant and persistent bacterial pathogens.

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Introduction

Antibiotic-resistant bacteria are a significant public health concern . Universal and careless administration of antibiotics, and the inherent flexibility of microbes has increased the rate of development of multidrug-resistant microorganisms, which is threatening the proper management of disease [1,2]. Bacteria have developed strategies to evade the host immune system and persist [3,4]. It is not only the resistance to antibiotics that determines the capacity of pathogenic bacteria to survive and multiply in the human host. Rather it is a dynamic and complex of adaptive mechanisms that allow bacteria to deal with environmental stressors, such as antimicrobial agents and host immune defense [5,6]. The bacteria are exposed to various adverse environments during infection i.e. nutrient limitation, oxidative stress, antimicrobial peptides, and killing by immune cells. The successful pathogens have been able to develop elaborate ways to detect these challenges, and to react in a manner that enhances their survival and continuity [7,8]. Traditionally, the bacterial adaptation studies have focused on antibiotic resistance. Nevertheless, there is a growing body of evidence that resistance is not a comprehensive explanation of the resistance and recurrence of most infections. Recent studies have focused on bacterial strategies, including immune manipulation and persistence. The strategies enable the bacteria to avoid immune surveillance, to regulate inflammatory reaction and to endure contact with the antibiotics without any irreversible genetic alterations [9,10]. The persistence in microbes such as biofilm formation or development of dormant or slow growing per sister cells is very vital in chronic and recurrent infections. These mechanisms allow the bacterial populations to cope with the killer conditions in the short run which lead to the treatment failure and extended disease courses. Notably, these persistence mechanisms tend to interact with an antibiotic resistance and immune evasion leading to a complicated system of survival mechanisms [11,12]. The purpose of the review is to absorb the existing information on the adaptive mechanisms of human pathogenic bacteria, especially antibiotic resistance and host immune manipulation and microbial persistence. Taking a comprehensive look at these processes, and not focusing on them separately, this review aims to

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bring a better insight into the existence of bacteria in the host and to point out the possible directions to which more effective therapy and preventive strategies may evolve [13,14].

Overview of Human Pathogenic Bacteria and Selective Pressures

Bacteria face adverse environments during infection, including nutrient limitation, oxidative stress, and immune attack. These pathogens comprise Gram-positive and Gram-negative bacteria, obligate and facultative intracellular organisms and species with highly diverse metabolic flexibility and virulence potential [15,16]. Nevertheless, irrespective of such diversity, one common attribute to all successful human pathogens is their capacity to respond to selective forces both in-vitro and in-vivo within a short time frame [17,18].

The pathogenic bacteria are subjected to selective pressures that occur in different sources. Bacteria in the human host are confronted with difficult challenges posed by natural and adaptive immune responses [19,20]. These are physical barriers which are the epithelial surfaces, chemical defenses like antimicrobial peptides and cellular defenses which include phagocytosis, oxidative burst and cytokine mediated inflammation .Only when they are able to fill a nutrient niche will exogenous bacteria be able to invade the intestine. Through a variety of strategies, including food competition, the healthy gut microbiota completely occupies these niches and stops pathogen intestinal invasion [21,22]. In order to endure such environmental conditions, pathogens have also evolved ways of detecting environmental signals and varying gene expression, which enables them to adjust metabolism, virulence and stress response pathways (figure1) [23,24].

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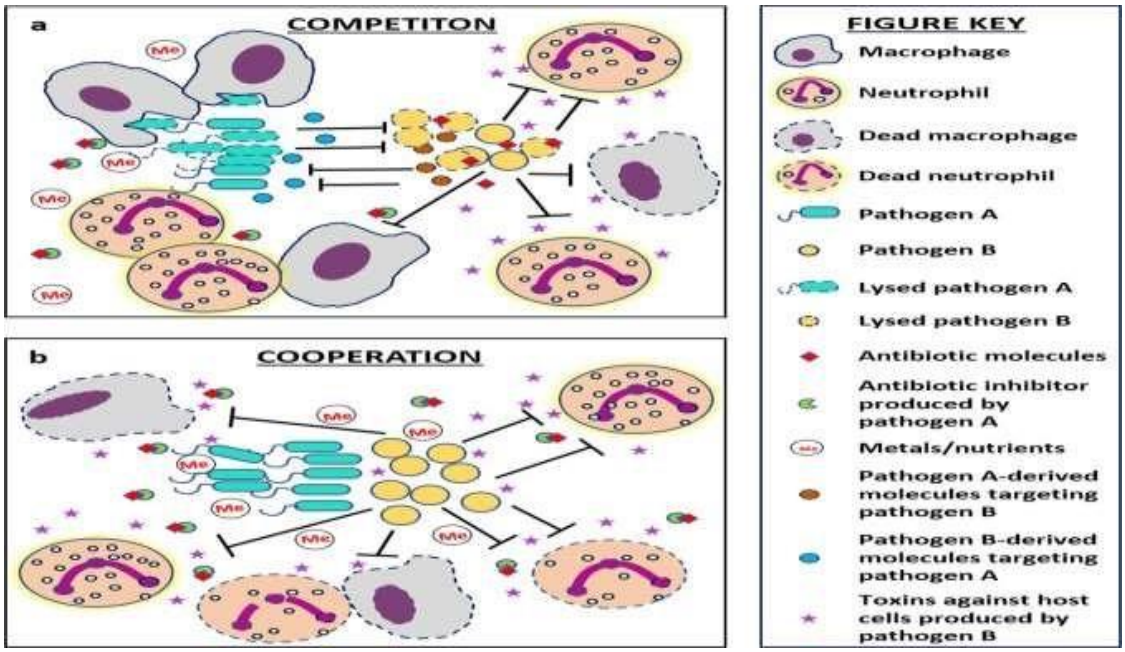

Figure 1. Selective pressures influencing the evolution of human pathogenic bacteria in the host environment.(A) Host-imposed selective pressures during infection, such as innate and adaptive immune responses, nutrient constraints, oxidative stress and competition with the host microbiota. (B) Pressures in treatment and stress, especially exposure to antibiotics, which induce bacterial stress reactions, tolerance, and development of adaptive mechanisms of survival.

Other than the host, anthropogenic pressures are the important factors that influence bacterial evolution. The intensive application of antibiotics in the clinical medicine, agriculture, and animal husbandry sectors has resulted in formidable selective pressure in favor of resistant and tolerant bacterial communities [25]. The selection of adaptive characteristics that increase survival in the absence of conferring classical resistance, especially in response to exposure to sub-lethal concentrations of antibiotics, is facilitated by exposure to sub-lethal concentrations of antibiotics. These external forces are frequently associated with genetic diversification by mutation and horizontal gene transfer which allow the rapid transfer of adaptive phenotypes among bacterial communities [26,27]. Notably, selective pressures do not work independently but will dynamically interact throughout the process of infection. As an example, immune stress can cause bacterial stress responses, which both increase antibiotic tolerance and antibiotic exposure can change bacterial surface structures in a manner that influences immune recognition. This network of selective pressures gives rise to the complex adaptive phenotypes such as

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immune evasion, persistence and resistance [28,29]. It is necessary to comprehend the nature and origins of such selective pressures to understand its mode of adaptive strategies in the following sections. It gives us a conceptual model of valuing the integration of environmental cues by pathogenic bacteria to maximize survival, colonization and prolonged persistence in the human host (figure 2) [30,31].

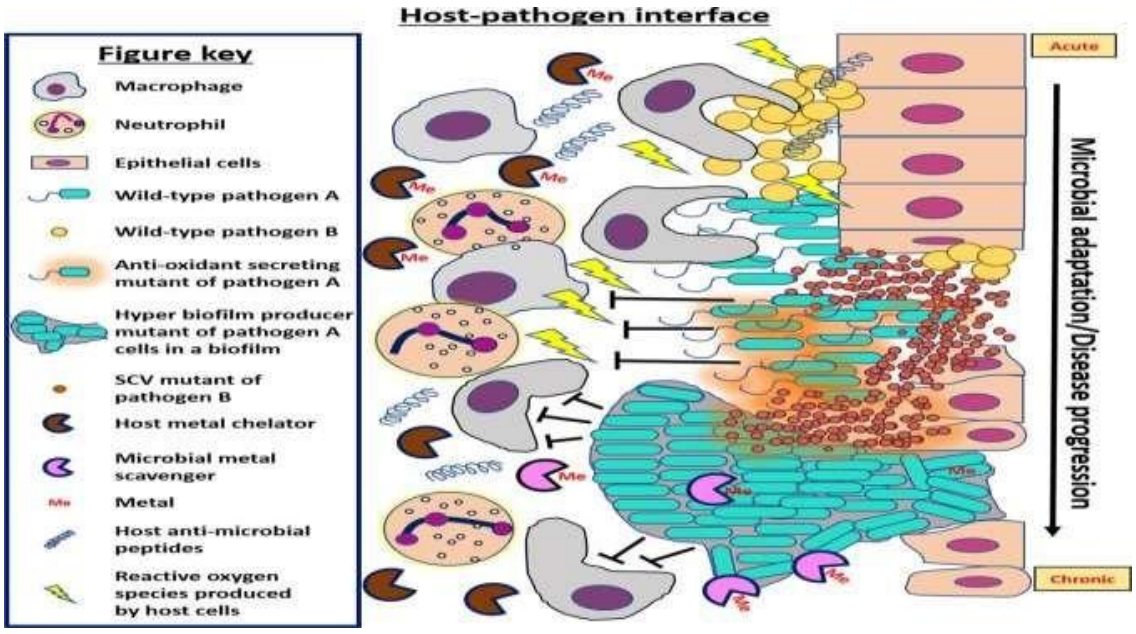

Figure 2. Integrated host–pathogen interactions driving bacterial survival and adaptation.

Antibiotic Resistance Mechanisms in Pathogenic Bacteria

Antibiotic resistance involves target modification, enzymatic inactivation, efflux pump overexpression, and horizontal gene transfer [32]. Summarizes the major antibiotic resistance mechanisms employed by human pathogenic bacteria **(**Table1) [33]**.** One of the primary effects of the intense selection pressure brought about by the widespread use of antibiotics in the clinical, agricultural, and environmental settings is the emergence of resistance mechanisms. Even in the presence of antimicrobial treatments that seek to eradicate them, these activities aid in the survival, growth, and multiplication of bacteria [34]. Alteration of antibiotic targets is one of the most frequently used resistance mechanisms in which mutation or enzymatic changes cause a loss of drug binding affinity. They include changes in penicillin-binding proteins in -lactam resistance, and changes in ribosomal changes which cause macrolide and aminoglycoside

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resistance[35,36]. The other predominant process is enzymatic deactivation of antibiotics, including the formation of β -lactamases that dismantle β -lactam antibiotics, making them inactive. The β -lactamases with extended spectra [ESBLs] and carbapenems are particularly dangerous because they are widespread in terms of their activity towards last-resort antibiotics [37]. Another method that bacteria use to evade antibiotics is the active expression of efflux pumps through which the bacterium can physically remove antibiotics in the cell and reduce the drug concentration to non-lethal levels. These pumps are either a highly specific pump or multidrug in nature, which may lead to cross resistance to various classes of antibiotics. Further, decreased membrane permeability, and especially in Gram-negative bacteria, restricts entry of antibiotics by altering porins and outer membrane proteins [38,39] .One of the main reasons that have increased the rate of resistance spread is horizontal gene transfer which enables a resistance determinant to propagate fast through plasmids, transposons and integrons. This procedure helps the development of the multidrug-resistant strains and makes the work of the infection control more complicated. Notably, antibiotic resistance is frequently accompanied with other adaptive behaviors such as immune avoidance and persistence, which point to their combination in a larger survival strategy but not as a singular phenomenon [40,41].

Table 1. Major antibiotic resistance mechanisms in human pathogenic bacteria

Resistance mechanism	Description	Representative examples
Target modification	Structural alteration of antibiotic targets	Altered PBPs in *Streptococcus pneumoniae*
Enzymatic inactivation	Enzymes degrade or modify antibiotics	β-lactamases in *Escherichia coli*
Efflux pumps	Active removal of antibiotics from the cell	AcrAB-TolC in Gram-negative bacteria
Reduced permeability	Decreased antibiotic uptake	Porin loss in *Pseudomonas aeruginosa*
Horizontal gene transfer	Spread of resistance genes between bacteria	Plasmid-mediated carbapenemases

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Bacterial Strategies for Host Immune System Manipulation

Pathogens also manipulate host immune responses to evade detection and enhance colonization .The host immune system controls bacterial infections but can also contribute to tissue damage. Bacteria can manipulate the host immune response to promote survival. The host immune system recognizes bacterial pathogens through immune cell activation [42,43].Bacteria evade the host immune system by producing immune evasion proteins. Other pathogens also produce proteins that block the activation of complement that inhibit opsonization and phagocytosis(Table 2) [44,45]. Pathogenic bacteria can actively suppress or regulate the immune responses by disrupting the activity of cytokines signaling and immune cells. As an example, some bacteria inject effector proteins into cells of the host by specific secretion systems, and cause interference with intracellular signaling cascades that respond to inflammation and antimicrobial activity. By producing anti-inflammatory cytokines or immune cell death, numerous pathogenic bacteria control host immunity, fostering an environment that is favorable to their survival. [46,47]. Intracellular pathogens survive inside host cells, such as macrophages and epithelial cells, avoiding antibodies and antibiotics. These bacteria can change the maturation of the phagosomes or oxidative killing, which makes the immune cells protective niches. Notably, the immune manipulation tends to increase the bacterial persistence and the chronic infection, which is part of the recurrence and chronic colonization [48,49]. Host-pathogen interactions are complicated by the interplay between immune evasion and other adaptive mechanisms, including antibiotic resistance and persistence. These mechanisms of immune manipulation would help in understanding how to devise therapies that would reestablish a proper immune response and supplement antimicrobial therapy [50].

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Table 2. Key mechanisms of immune system manipulation by pathogenic bacteria

Immune manipulation strategy	**Mode of action**	**Representative pathogens**
Antigenic variation	Alters surface antigens to evade recognition	*Neisseria gonorrhoeae*
Capsule formation	Prevents phagocytosis	*Streptococcus pneumoniae*
Complement inhibition	Blocks complement-mediated killing	*Staphylococcus aureus*
Secretion of effector proteins	Disrupts host immune signaling	*Salmonella enterica*
Intracellular survival	Avoids immune clearance within host cells	*Mycobacterium tuberculosis*

Microbial Persistence and Survival Mechanisms

Microbial persistence mechanisms, including biofilm formation and persister cells, help bacteria withstand treatments. Bacteria can survive in the host environment by forming biofilms and producing virulence factors that aid colonization. These processes are prominent in chronic, recurrent and treatment-refractory infections [51]. One of the most well-defined persistence mechanisms is biofilm formation, in which bacterial cells embed themselves in an extracellular matrix composed of proteins, polysaccharides, and extracellular DNA. In addition to creating micro habitats with minimal nutrition supply and oxygen gradient, biofilms provide physical resistance to immune effector molecules and antibiotics. Since most antimicrobial drugs target cell divisions in active growth, these conditions promote slack growth or dormancy, rendering most antibiotics ineffective [52,53]. The other significant persistence strategy is that of the formation of persister cells which is a small minority of dormant or metabolically inactive cells capable of enduring lethal antibiotic concentration. Persister cells are genetically identical to other members of the bacterial population but have transient tolerance, which has been attributed to changed states of metabolism and stress-response. These cells are capable of resuscitation and repopulation upon the removal of the antibiotic pressure, hence causing infection relapse [54,55].

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Stress response pathways that are used by pathogenic bacteria to acclimatize to nutrient limitation, oxidative stress, and immune attack include toxin-antitoxin systems and stringent response signaling. These control systems enable bacteria to promptly shift to survival where growth goes into the background. Notably, the mechanism of persistence can persist along with antibiotic resistance and immune evasion causing overlapping defense measures that improve long-term survival in the host [56,57]. The concept of microbial persistence plays a critical role in treating chronic infections due to the inability of traditional antibiotic treatment to kill the enduring bacterial communities. Attack on the persistence-related mechanisms can be thus a promising approach to enhancing treatment outcomes [58]. Tolerance is the ability of a whole bacterial population to withstand extended treatment to a bactericidal antibiotic without the minimum inhibitory concentration (MIC) changing is known as tolerance. Tolerant cells do not proliferate during treatment, but they need to be exposed for a longer period of time in order to be destroyed (i.e., a greater minimum duration for death[59]. Persistence Only a tiny subset of bacteria, known as persister cells, can withstand high antibiotic concentrations in persistence, a particular type of tolerance that produces a biphasic death curve (rapid murder of most cells + slow survival of persisters). These survivors can regenerate after the antibiotic is stopped and are phenotypically tolerant but do not exhibit an elevated MIC [60] .The HipBA and MazEF systems are two examples of toxin-antitoxin (TA) systems, which are important for bacterial persistence. In Escherichia coli, the MazEF system promotes growth arrest and programmed cell death in response to environmental stress, whereas the HipBA system controls the development of persister cells under antibiotic treatment [61].

Interconnection Between Resistance, Immune Evasion, and Persistence

Emerging evidence indicates that antibiotic resistance, immune evasion, and microbial persistence are not independent adaptive strategies, but rather interconnected processes that function as an integrated survival network. Pathogenic bacteria coordinate these mechanisms to enhance their ability to withstand both antimicrobial therapy and host immune defenses [62,63]. Antibiotic exposure plays a central role in this interplay. Sub-inhibitory concentrations of antibiotics can modulate bacterial gene expression, leading to alterations in surface antigens, virulence factors, and biofilm formation. These changes reduce immune recognition and promote

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persistent infections. Conversely, immune-mediated stresses—such as reactive oxygen species and antimicrobial peptides—can induce bacterial stress responses that enhance antibiotic tolerance [64,65]. Resistance and persistence are also closely linked at the metabolic level. Resistance mechanisms may reduce the metabolic burden imposed by antibiotics, enabling bacteria to allocate resources toward survival rather than rapid growth. In parallel, persistence prolongs bacterial survival under antibiotic pressure, increasing the likelihood of acquiring resistance through mutations or horizontal gene transfer [66,67].Immune evasion further strengthens this adaptive network by allowing bacterial subpopulations to escape clearance. Intracellular survival is a key example, as bacteria residing within host cells are protected from both immune attack and antibiotic exposure. These intracellular niches can support the development of specialized phenotypes, such as small colony variants, which enhance survival under hostile conditions and contribute to recurrent and persistent infections [68–69]. The pmr (pmrA/pmrB) operon in Gram-negative bacteria is a well-studied illustration of this molecular interaction. When this system is activated, lipid A undergoes changes such the addition of phosphoethanolamine or L-Ara4N. These modifications lower the outer membrane's negative charge, which reduces polymyxin binding and confers antibiotic resistance while also hindering TLR4-mediated immune detection and encouraging immune evasion [70]. Importantly, despite seeming in vitro susceptibility, bacteria in biofilms or persister states can withstand antibiotic treatment without developing genetic resistance, which frequently results in treatment failure and illness recurrence. This demonstrates the shortcomings of existing diagnostic techniques and emphasizes the necessity of standardized procedures that can identify these phenotypes [71]. Therapeutic approaches that focus on a particular pathway are unlikely to be successful due to the interconnectedness of various systems. Combination techniques, on the other hand, have more potential to improve treatment outcomes and limit pathogen adaptation within the host by concurrently disrupting numerous bacterial activities, such as metabolic pathways, resistance mechanisms, and immune evasion strategies [72–73].

Conclusion and Future Perspectives

Bacteria that pose a danger to humans have an impressive adaptation potential, and thus they can stay alive and reproduce under heavy selection pressure associated with antimicrobial treatment and the immune system of a human host. The current review also outlines that antibiotic

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resistance, manipulation of the host immune, and microbial persistence all play a role in bacterial survival, chronicity of diseases and treatment failure. These, adaptive strategies are not phenomena that appear in isolation but rather related processes that support each other and make it more difficult to handle infections. The molecular connections between resistance, immune evasion and persistence should be unraveled in future studies in order to find areas of vulnerability that can be utilized as a point of therapy. New antimicrobials, anti-virulence agents, and immunomodulatory therapies are developing and will have a role to play especially in combination with methods to address biofilms and persister cells. Besides, better antibiotic stewardship and infection control practices are also necessary to minimize the selective pressure and the transmission of adaptive bacterial characteristics. An in-depth insight into bacterial adaptability will play a very significant role in solving the increasing threat of persistent and resistant infections on the global front. Novel therapies are needed to improve public health and reduce infectious disease burden.

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