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PATHOGENIC RESPONSE MECHANISMS TO HOST AND THERAPEUTIC STRESS: CHALLENGES IN ADVANCED MEDICAL MICROBIOLOGY

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Abstract

Pathogens employ a diverse array of sophisticated mechanisms to survive the hostile conditions imposed by host immune defenses, antimicrobial therapies, and clinical environments. This review examines critical adaptive strategies-including oxidative stress resistance, iron acquisition, biofilm formation, and horizontal gene transfer -that enable high-priority pathogens such as Mycobacterium tuberculosis, Candida albicans, Pseudomonas aeruginosa, and methicillin-resistant Staphylococcus aureus (MRSA) to evade immune clearance, persist in host tissues, and develop multidrug resistance. In healthcare settings, additional stressors - such as disinfectant exposure, nutrient limitation, and prolonged or inappropriate antibiotic use - exert strong selective pressure, driving the emergence of resilient organisms like carbapenem-resistant Enterobacteriaceae and Clostridioides difficile. These adaptations operate through both rapid, reversible responses (e.g., morphological switching in C. albicans or efflux pump upregulation in P. aeruginosa) and long-term genetic changes, including mutations (e.g., rpoB mutations conferring rifampin resistance in M. tuberculosis) and horizontal gene transfer-mediated dissemination of resistance genes via plasmids. Biofilm formation further complicates treatment by creating structured, metabolically heterogeneous communities that shield microbes from antibiotics and immune effectors—particularly on indwelling medical devices.

To counter these evolving threats, innovative approaches are essential. Advanced diagnostics, including whole-genome sequencing and CRISPR-based platforms (e.g., SHERLOCK), enable real-time surveillance and precise identification of resistance markers. Therapeutically, quorum sensing inhibitors and antivirulence agents offer promising alternatives that disrupt pathogenicity without exerting strong selective pressure for resistance. Combination therapies and emerging delivery systems, such as nanoparticles, enhance drug efficacy and penetration. Equally critical are robust infection prevention and control measures to curb hospital-acquired infections, which impose substantial clinical and economic burdens globally.

With antimicrobial resistance directly responsible for 1.27 million deaths in 2019 and undermining progress toward the Sustainable Development Goals, a coordinated, One Health-informed response is imperative. Integrating genomics, proteomics, bioinformatics, and public health policy will be key to developing precision interventions that anticipate and outmaneuver pathogen adaptation in an era of escalating AMR and emerging zoonotic diseases.

Keywords: *pathogenic adaptation, antimicrobial resistance, riofilm formation, oxidative stress resistance, horizontal gene transfer (HGT), quorum sensing inhibition, hospital-acquired infections.*

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Introduction

Microbial adaptation to host and therapeutic stress is a fundamental aspect of medical microbiology, directly influencing infection outcomes and the effectiveness of treatments [*Hauser et al. 2011*]. Pathogens employ a variety of strategies to survive in challenging conditions, including evading immune responses and adapting their metabolism in response to host-imposed nutrient limitations [*Murdoch & Skaar, 2022*]. The emergence of multidrug-resistant pathogens (**Table 1**), such as carbapenem-resistant *Klebsiella pneumoniae* and methicillin-resistant *Staphylococcus aureus* (MRSA), highlights the critical importance of these adaptive mechanisms. Additionally, infections involving biofilms on medical devices and persistent forms like antibiotic-tolerant *Mycobacterium tuberculosis* further complicate clinical management [*Sarangi et al. 2024*].

Microorganisms have developed diverse and highly specialized strategies to adapt to harsh environments, a key concern in medical microbiology. These adaptations enable pathogens to thrive despite host immune defenses, therapeutic interventions, and environmental stressors commonly encountered in healthcare settings. Notable pathogens such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Mycobacterium tuberculosis* illustrate how these adaptive responses contribute to persistent infections and resistance to treatment [*Sarangi et al. 2024*].

Adaptation occurs through both short-term and long-term mechanisms. Short-term responses include rapid genetic and epigenetic changes, such as alterations in gene expression regulated by stress-responsive sigma factors and transcriptional reprogramming. Long-term adaptations, on the other hand, are driven by genetic mutations and horizontal gene transfer, which allow pathogens to acquire resistance traits and enhance virulence. For example, *Klebsiella pneumoniae* has exhibited remarkable adaptability by acquiring carbapenemase genes, which enable it to resist carbapenem antibiotics, contributing to widespread multidrug-resistant outbreaks [*Yan et al. 2017; Bari et al. 2022*].

Now accumulation to adapting to antimicrobial agents, pathogens also adjust to the immune pressures within their hosts. They deploy a range of complex strategies, including biofilm formation, immune evasion, and metabolic flexibility, to establish and maintain persistent infections. Biofilms, in particular, serve as a physical and metabolic barrier, shielding pathogens from both host immune responses and antibiotic treatments. Chronic infections caused by *Pseudomonas aeruginosa* in cystic fibrosis patients are a prime example of the clinical challenges posed by biofilm-associated infections.

External pressures within healthcare environments also contribute to the evolution of resistant and resilient pathogens. Frequent exposure to disinfectants, prolonged and inappropriate antibiotic use, and the increasing invasiveness of modern medical procedures create conditions where microbial adaptation can flourish.

The rising prevalence of antimicrobial resistance (AMR) underscores the urgency of addressing these adaptive mechanisms (**Table 2**). For AMR other details Pathogens like *Mycobacterium tuberculosis* exploit dormancy and persistence strategies to evade antibiotics and immune detection, leading to chronic and hard-to-treat infections. A deeper understanding of these mechanisms is

Table 1.

Priority Pathogens Based on Antibiotic Resistance and Sustainable Development Goals (at a crossroads)

Priority	Pathogen	Key Resistance Mechanisms
Critical	Acinetobacter baumannii	Carbapenem-resistant
	Pseudomonas aeruginosa	Carbapenem-resistant
	Enterobacteriaceae	Carbapenem-resistant, ESBL (Extended-Spectrum Beta-Lactamase)-producing
High	Enterococcus faecium	Vancomycin-resistant
	Staphylococcus aureus	Methicillin-resistant, Vancomycin-intermediate/resistant
	Helicobacter pylori	Clarithromycin-resistant
	Campylobacter spp.	Fluoroquinolone-resistant
	Salmonellae	Fluoroquinolone-resistant
	Neisseria gonorrhoeae	Cephalosporin-resistant, Fluoroquinolone-resistant
Medium	Streptococcus pneumoniae	Penicillin-non-susceptible
	Haemophilus influenzae	Ampicillin-resistant
	Shigella spp.	Fluoroquinolone-resistant

Note: Priority pathogen list by WHO for developing new antibiotics

Table 2.

From: Antimicrobial resistance and Sustainable Development Goals: at a crossroads

Network Name	Focus Areas
North American	Human Medicine, Veterinary Medicine, Agriculture, Diagnosis, Data Science, Education, Evolution, Engineering
Southeast Asian	Environmental Sciences, Engineering, Genomics, Agriculture, Biology
East Asian	Biotechnology, Food Safety
South Asian	Human Medicine, Veterinary Medicine, Agriculture, Computer Science
African	Human Medicine, Chemistry
Latin American	Human Medicine, Microbiology

Note: Aspects of next generation AMR networking

essential for the development of innovative diagnostic tools, therapeutic strategies, and infection control measures [*Aslam et al. 2024*].

As microbial adaptation continues to drive major global health challenges, including the AMR crisis and the emergence of zoonotic diseases, interdisciplinary approaches integrating genomics, proteomics, and bioinformatics are increasingly vital. These technologies not only enhance our understanding of pathogen behavior but also enable the development of precision medicine and tailored therapeutic interventions, marking a critical shift in the fight against infectious diseases.

Antimicrobial resistance is a critical global health challenge with far-reaching implications, including hindering progress toward achieving the Sustainable Development Goals (SDGs). Recent estimates reveal that in 2019, AMR directly caused 1.27 million deaths worldwide, with an additional 4.95 million deaths indirectly linked to AMR-related infections. Recognizing the gravity of the issue, the World Health Organization (WHO) designated AMR as a major global health threat in 2014 [*Imran et al. 2023*]. In response, the World Health Assembly introduced the Global Action Plan on Antimicrobial Resistance, urging member states to adopt and implement national action plans by May 2017. Strategies such as the prudent use of antimicrobial agents have been promoted to curb the emergence and spread of AMR [*Mohammad et al. 2023*].

FACTORS INFLUENCING PATHOGENIC ADAPTATION

Host-Imposed Stress

Pathogens face numerous stressors within host environments, including oxidative bursts, nutrient deprivation, and immune system targeting. These pressures drive sophisticated adaptations:

a. Oxidative Stress Resistance: Host immune cells, particularly macrophages and neutrophils, generate reactive oxygen species and reactive nitrogen species (RNS) as part of their antimicrobial arsenal. To counteract this, *Mycobacterium tuberculosis* produces catalase-peroxidase (KatG), which neutralizes hydrogen peroxide, a precursor to reactive oxygen species. This enzymatic defense is crucial for its survival in the oxidative milieu of macrophages [*Chandra et al. 2024*].

b. Morphological and Phenotypic Adaptation: Pathogens such as *Candida albicans* alter their morphology (from yeast to hyphal form) to evade immune detection and establish infection niches **(Table 3).** This morphological switch is regulated

Table 3.

Pathogen Adaptation Mechanisms and Their Complexity

Adaptation Mechanism	Pathogens Affected	Adaptive Response	Complexity of Response
Oxidative Stress Resistance	*Mycobacterium tuberculosis*	Catalase production to neutralize reactive oxygen species (ROS)	Moderate
Iron Acquisition	*Escherichia coli*	Siderophore production to scavenge iron	Moderate
Morphological Change (Candida albicans)	*Candida albicans*	Switch from yeast to hyphal form to evade immune detection	High
Horizontal Gene Transfer	*Klebsiella pneumoniae, Enterobacteriaceae*	Gene transfer through plasmids (e.g., carbapenemases)	High
Efflux Pumps	*Pseudomonas aeruginosa*	Active expulsion of antibiotics using efflux pumps	High
Biofilm Formation	*Pseudomonas aeruginosa, Staphylococcus aureus, S. mutans*	Metabolic heterogeneity and structural protection within biofilms	Very High

by environmental cues such as pH, temperature, and nutrient availability.

c. Iron Acquisition Mechanisms: Hosts sequester iron as part of nutritional immunity, limiting its availability to pathogens. In response, microbes like *Escherichia coli* produce siderophores, high-affinity iron-chelating molecules, to scavenge iron from host proteins. Similarly, *Staphylococcus aureus* uses the Isd system to extract heme-bound iron from hemoglobin.

Antimicrobial Pressure

The excessive use of antibiotics has given rise to numerous antibiotic-resistant bacteria, including strains capable of thriving in environments where antibiotics serve as their sole carbon source. This extraordinary development highlights the robust and diverse resistance mechanisms in certain bacterial strains. Additionally, many of these strains exhibit hypermutator phenotypes and possess the ability to transmit virulence, facilitating the spread of their genomic and proteomic traits and enhancing their pathogenic potential:

a. Mutation-Induced Resistance: Mutations in key genes confer resistance. For instance, *Mycobacterium tuberculosis* acquires mutations in the *rpoB* gene, altering RNA polymerase and reducing rifampin binding efficiency [*Woappi et al. 2016*].

b. Horizontal Gene Transfer: Resistance genes, such as those encoding beta-lactamases, are frequently shared between bacterial populations through conjugation, transformation, and transduction. *Enterobacteriaceae*, for example, disseminate carbapenemase genes via plasmids, creating a reservoir of resistance in both clinical and community settings [*McInnes et al. 2020*].

c. Efflux Pumps: Bacteria use efflux pumps to actively expel antibiotics, reducing intracellular drug concentrations. *Pseudomonas aeruginosa* exhibits upregulation of the MexAB-OprM efflux system, conferring resistance to multiple drug classes. Active efflux systems may be responsible for resistance to several chemically distinct antibiotics and bactericides, with alarming numbers of occurrences in environmental and clinical isolates [*Lorusso et al. 2022*].

Clinical and Environmental Stressors

Various factors influence a pathogen's ability to establish persistent infections, encompassing both host and bacterial elements. Some pathogens, such as *Salmonella Typhi* and others mentioned in Table 3, are particularly adept at evading the host immune system, allowing them to persist in infected individuals for decades without causing symptoms. In contrast, pathogens like *Escherichia coli* and *Pseudomonas aeruginosa* can lead to both acute and chronic infections, with specific changes in the host environment enabling the development of persistent infections [*Grant et al. 2013*].

a. Exposure to Disinfectants and Antiseptics: Frequent use of chemical agents like quaternary ammonium compounds selects for resistant strains. For example, *Acinetobacter baumannii* adapts by altering membrane permeability and upregulating efflux pumps, enabling it to survive harsh cleaning protocols [*Boyce 2023*].

b. Limited Nutrient Availability: In clinical environments, nutrient scarcity forces pathogens to adapt metabolically. *Clostridioides difficile*, a notorious cause of Hospital-acquired infections, modifies its metabolic pathways to utilize alternative carbon sources in nutrient-deprived settings.

c. Biofilm Formation: Biofilms enhance microbial resistance to antibiotics and disinfectants. Within biofilms, gradients in oxygen and nutrient availability lead to metabolic diversity, allowing subpopulations to survive otherwise lethal conditions. This is particularly problematic in infections involving indwelling medical devices [*Mohammad et al. 2023; Imran et al. 2024*].

d. Selective Pressure from Antimicrobial Use: Prolonged and inappropriate antibiotic use in hospitals promotes the emergence of multidrug-resistant pathogens. *Enterococcus faecium*, for instance, has adapted to survive vancomycin treatment by acquiring vanA and vanB genes through plasmid transfer.

APPLICATIONS IN MEDICAL MICROBIOLOGY

Therapeutic Innovations

Advancements in understanding how pathogens adapt to stressors have fueled the development of targeted therapies to combat infections effectively. Here's a detailed look:

a. Quorum Sensing Inhibitors: Quorum sensing (QS) is a cell-to-cell communication system in bacteria that regulates biofilm formation, virulence factor production, and stress response. QS inhibi-

tors aim to disrupt these communication pathways, thereby reducing pathogenicity and biofilm resilience [*Holm & Vikström 2014*].

• *Examples:* Molecules like furanones inhibit QS in *Pseudomonas aeruginosa*, reducing biofilm-associated infections.

• *Applications:* They are promising in managing infections where biofilms, such as those on catheters or prosthetics, resist conventional antibiotics [*Lee et al. 2013*].

b. Antivirulence Drugs: Antivirulence therapies target pathogen-specific factors like toxins and adhesion molecules instead of outright killing the microbe. This reduces selective pressure for resistance [*Dickey et al. 2017*].

• *Mechanisms:* Drugs that inhibit toxin production (e.g., antitoxins against *Clostridium difficile*) or disrupt bacterial adhesion (e.g., anti-adhesion peptides) have shown efficacy.

• *Benefits:* Unlike traditional antibiotics, these drugs do not disturb the host microbiota.

c. Combination Therapies: Combining drugs with complementary mechanisms of action enhances efficacy and prevents resistance. The common of the data assessing combination therapy were determined using in vitro techniques or animal models of infection. Over analyses of this information, combined with the presented clinical data, albeit partial, it is possible to identify a number of clinical situations where combination therapy can be maintained [*Hagihara et al. 2012*].

• *Examples:* Using colistin with meropenem against carbapenem-resistant *Enterobacteriaceae* has shown success in clinical trials.

• *Future Directions*: Nanoparticle-based delivery systems are being explored to improve the targeted delivery of combination therapies.

Diagnostics

Rapid and precise diagnostics are pivotal for personalized medicine and infection control. Intracranial infection and hemorrhagic cerebro spinal fluid are manipulating factors for prominent cerebro spinal fluid PCT resulting neurosurgery. It should be noted that the diagnostic assessment of intracranial infection by cerebro spinal fluid PCT elevated alone is limited, but the combination it with other indicators can help advance diagnostic efficacy [*Wang et al., 2023*]. Advances include:

a. Genomic Tools: Whole-genome sequencing and metagenomics enable comprehensive identification of pathogens and resistance genes [*Pritchard et al., 2016*].

• ***Applications****:* Whole-genome sequencing is used in real-time surveillance of AMR outbreaks, such as in *Mycobacterium tuberculosis*.

• ***Innovations****:* CRISPR-based diagnostics (e.g., SHERLOCK) offer high sensitivity for detecting specific resistance mutations.

b. Proteomic Approaches: Mass spectrometry tools like MALDI-TOF rapidly identify pathogens by analyzing protein profiles. Proteomic data support hypotheses generated by genomic data in addition to suggesting future mechanistic studies, indicating that future whole-genome sequencing studies be designed to leverage proteomics as a critical complement [*Leiser et al. 2015*].

Benefits: These methods are faster than traditional cultures and allow clinicians to tailor antibiotic therapies.

c. Point-of-Care Testing: Point-of-care testing devices facilitate bedside diagnostics, offering quick detection of pathogens like *Streptococcus pneumoniae* and resistance markers like ESBLs. This review highlights numerous factors affecting point-of-care testing use in primary care. Policymakers planning to implement point-of-care testings are likely to achieve more by providing multifaceted interventions that target factors outside, within, and post-consultation [*Hoste et al. 2024*].

Infection Control

Hospital-acquired infections are a significant public health concern, contributing to increased mortality, morbidity, prolonged hospital stays, and substantial healthcare costs. In Europe alone, hospital-acquired infections result in 16 million additional hospitalization days annually, with costs exceeding 7 billion euros.

Early identification and diagnosis of hospital-acquired infections, guided by standardized definitions, are essential for effective case management, Numbers are well distributed and labelled in **Figure 1**. To accurately assess the scale of the problem and ensure the consistent implementation of preventive measures, it is crucial that all cases are systematically reported [*Voidazan et al. 2020*].

Controlling hospital-acquired infections is a

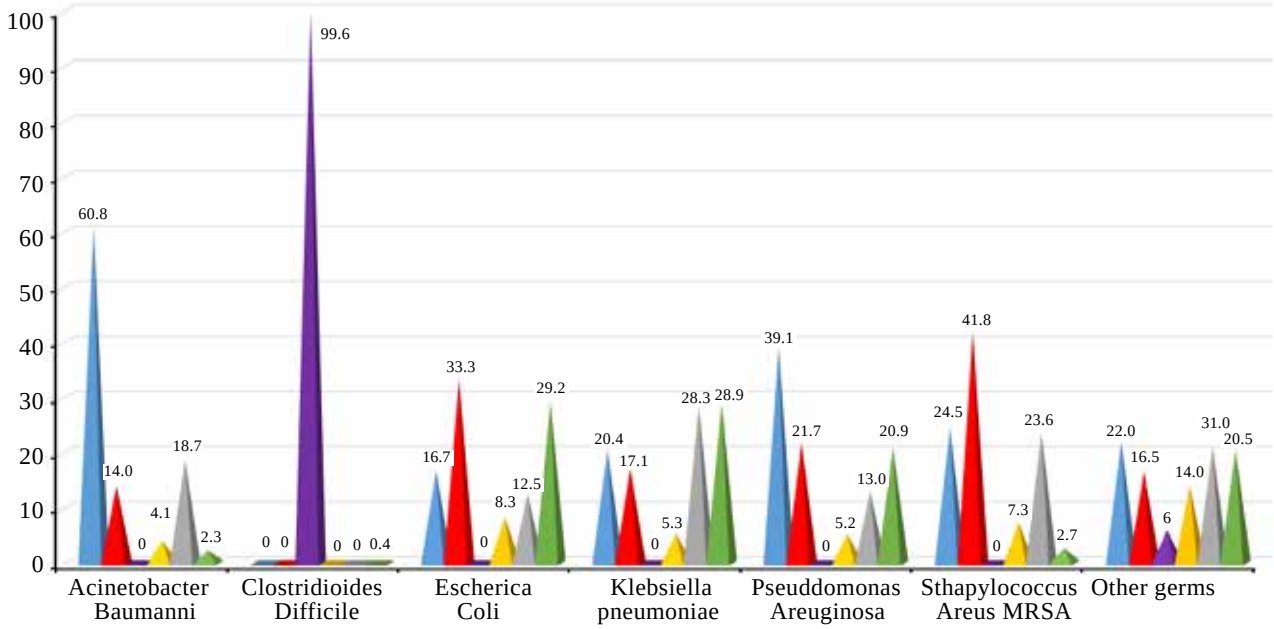

Figure 1*. Identification of HAI and type of pathogen* [*Voidazan et al. 2020 (Int. J. Environ. Res. Public Health) resistance* [*Kunnath et al. 2024 (Br J Biomed Sci)*], *where: -Bronchopneumonia, - Enterococitis Clostridioides difficile, - Sepsis, - Surgical wound infection, - Other infections, - Urinary infection*

priority due to their persistence in healthcare settings. Key strategies include:

a. Optimized Sterilization: Effective disinfection and sterilization practices are vital to prevent the transmission of infectious pathogens through medical and surgical instruments or environmental surfaces. With the continuous evolution of technologies and products in healthcare settings, maintaining robust sterilization protocols remains crucial [*Rutala et al. 2023*].

In healthcare facilities, disinfection and sterilization processes are categorized based on the intended use of items: cleaning, low-level disinfection (for devices and surfaces that contact intact skin), high-level disinfection (for semicritical items that contact mucous membranes), and sterilization (for critical items such as surgical instruments that contact sterile tissue).

• Using advanced sterilization techniques, such as plasma-based systems, ensures effective elimination of resilient biofilms and spores.

• Adoption of ultraviolet (UV) disinfection robots in operating rooms is on the rise [*Rutala et al. 2023*].

b. Antimicrobial Stewardship: Infections caused by antibiotic-resistant bacteria are linked to higher morbidity, mortality, and increased healthcare costs. An effective antimicrobial stewardship program (ASP) aims to optimize clinical outcomes, reduce antimicrobial-related toxicity, and curb the emergence of resistance. By achieving these objectives, ASPs help lower healthcare costs while maintaining or enhancing the quality of care [*Taplitz et al. 2016*].

Examples: Initiatives to limit broad-spectrum antibiotic use in intensive care units are critical for preserving last-line drugs like colistin.

c. Enhanced Surveillance: A study of U.S. general hospitals revealed that implementing intensive infection surveillance and control programs significantly reduced nosocomial infections, including urinary tract infections, surgical wound infections, pneumonia, and bacteremia, between 1970 and 1975–1976. These reductions were observed even after accounting for variations in hospital and patient characteristics [*Haley et al. 1985*].

Key components of successful programs included organized surveillance and control activities, a dedicated infection control physician, one infection control nurse per 250 beds, and a system for reporting infection rates to practicing surgeons. Hospitals with these elements reduced their infection rates by 32%. However, since few hospitals had highly effective programs, only 6% of the estimated 2 million nosocomial infections in the mid-1970s were being prevented, leaving 26% poten-

tially avoidable with widespread adoption of such measures. In contrast, hospitals lacking effective programs experienced an 18% increase in infection rates during the same period [*Haley et al. 1985*].

EMERGING CHALLENGES

PERSISTENCE AND RECURRENCE

Persisting infections often stem from biofilm resilience and the presence of persister cells—dormant variants that withstand antibiotic treatment. **Figure 2** illustrates this relationship for better understand, Numerous studies highlight that bacterial cell persistence, marked by antibiotic tolerance, plays a dual role in treatment failure and in driving the evolution of resistance [*Kunnath et al. 2024*].

• ***Mechanisms:*** Persister cells exploit stress response systems like toxin-antitoxin modules and stringent response pathways to evade killing.

• ***Impact:*** Chronic infections, such as prosthetic joint infections, require prolonged or repeated treatments.

ANTIMICROBIAL RESISTANCE (AMR) CRISIS

Antimicrobial resistance is a critical global public health challenge that impacts human, animal, and environmental health. Although AMR arises through natural evolutionary processes, its rapid emergence and spread are primarily driven by the overuse and misuse of antibiotics in both humans and animals. AMR poses significant threats to global health, food security, environmental sustainability, financial stability, and socio-economic development. Its consequences are extensive, including severe illnesses, prolonged hospital stays, increased healthcare costs, an overburdened healthcare system, reliance on costly second-line treatments, treatment failures, and heightened mortality rates [*Majumder et al., 2020*]. **Table 1** illustrates various adaptive mechanisms employed by pathogens, highlighting their complexity and role in resistance.

Causes: Overuse of antibiotics in medicine and agriculture accelerates resistance.

Global Impact

Infections by multidrug-resistant pathogens like carbapenem-resistant *Klebsiella pneumoniae* result in significant mortality.

Solutions: Development of alternative therapies, such as bacteriophage therapy and synthetic biology-based antimicrobials, is underway.

EMERGING PATHOGENS:

Why do bacterial pathogens continue to emerge? In viral diseases like severe acute respiratory syndrome (SARS) and HIV, antigenic drift driven by random mutations is a common mechanism for their evolution and spread. Bacteria, however, have relatively stable genomes, making divergence through random mutations less frequent. This raises the question: are we truly encountering new pathogenic species and strains, or are we merely uncovering the vast and diverse prokaryotic world? In hindsight, many emerging infectious diseases (EIDs) appear to be caused by bacteria that have long existed in the environment but have only recently come into human contact or remained undetected until now. Zoonotic and

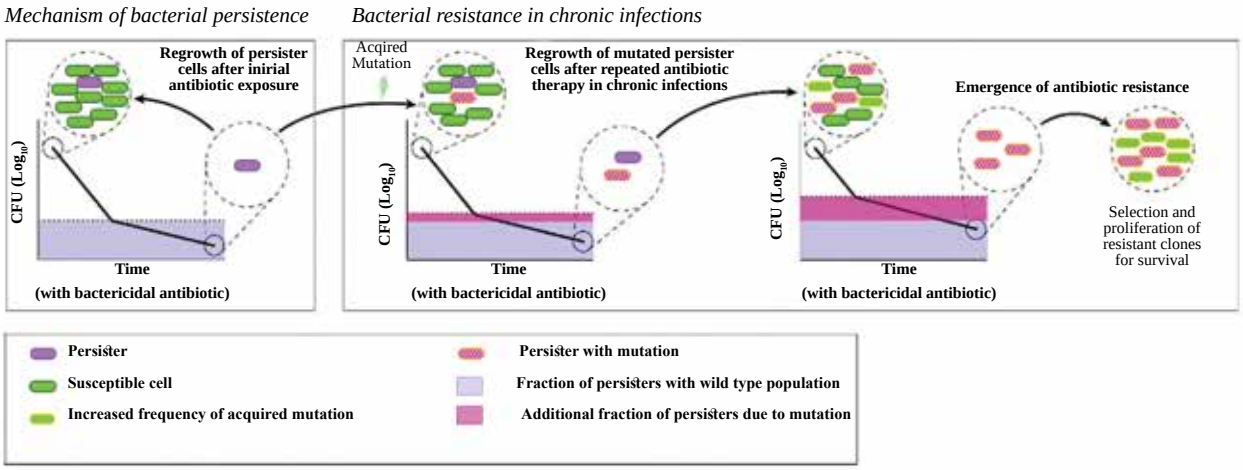

FIGURE 2. *Representation of bacterial persister cells acquiring mutations following repeated antibiotic treatments in chronic infections. These resistant clones undergo selective proliferation, leading to the development of antibiotic resistance [Kunnath et al. 2024 (Br J Biomed Sci)].*

environmental pathogens, such as *SARS-CoV-2* and *Ebola virus*, demonstrate the adaptability of pathogens to new hosts and environments [*Vouga & Greub 2016*].

Conclusion

Microbial adaptation to host and therapeutic stress plays a crucial role in the persistence and resistance of pathogens, complicating infection management. Pathogens like *Mycobacterium tuberculosis*, *Pseudomonas aeruginosa*, and *Candida albicans* use mechanisms such as oxidative stress resistance, biofilm formation, and horizontal gene transfer to survive and evade treatment. The rise of antimicrobial resistance and multidrug-resistant pathogens highlights the urgent need for novel therapeutic strategies, including quorum sensing inhibitors and combination therapies.

Advancements in diagnostics, such as whole-genome sequencing and point-of-care testing, are essential for rapid pathogen identification and personalized treatment. In healthcare settings, infection control measures like antimicrobial stewardship programs and advanced sterilization techniques are critical in combating resistant infections.

Given the growing challenge of AMR and emerging pathogens, an integrated "One Health" approach, along with continued global collaboration and research, is essential to address these threats. Understanding microbial adaptation mechanisms will drive the development of more effective treatments and improve patient outcomes in the face of evolving infectious diseases.

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