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Understanding antibiotic resistance: Challenges and solutions - A review article for healthcare staff

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***Abstract*---Background:** Antibiotic resistance (ABR) poses a critical threat to global health, with predictions indicating that by 2050, multi-drug resistant (MDR) infections could lead to approximately 10 million deaths annually, surpassing deaths from cancer and cardiovascular diseases. The overuse and misuse of antibiotics, particularly in agricultural settings, have exacerbated the issue. **Aim:** This review aims to provide healthcare staff with an understanding of the challenges posed by antibiotic resistance and explore potential solutions. **Methods:** A comprehensive literature review was conducted, analyzing historical and contemporary data on antibiotic discovery, resistance mechanisms, and current research initiatives aimed at addressing ABR. **Results:** Key findings indicate that the decline in new antibiotic development since the late 1980s, coupled with the rapid spread of resistance genes, has created an urgent need for novel therapeutic strategies. Recent research highlights promising compounds derived from natural sources, including marine fungi and Actinobacteria, which show potential against MDR pathogens. **Conclusion:** Immediate action is required to combat ABR, including improved antibiotic stewardship, public education, and increased funding for research into new antibiotics. Collaborative efforts among healthcare professionals, researchers, and policymakers are essential to address this escalating crisis.

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Introduction

In the absence of newly isolated antibiotics by the year 2050, the Centers for Disease Control (CDC) predicts that approximately 10 million deaths annually from multi-drug resistant (MDR) bacterial infections will occur worldwide, surpassing fatalities from cancer and cardiovascular diseases combined. Presently, infectious diseases rank as the second leading cause of mortality globally, and fourth in the United States, with 17 million deaths each year attributed to bacterial infections (Martens and Demain 2017). Despite this, awareness of antibiotic-resistant bacteria and its implications for global health remains alarmingly low among the general public. Notably, there have been no new classes of antibiotics developed for treating microbial infections in over three decades, as pharmaceutical companies have predominantly focused their research and development efforts on more profitable drugs for non-infectious conditions. Consequently, many large pharmaceutical firms have halted the discovery of novel products (NP), leaving academic institutions and small startups to pursue antibiotic therapeutics (Hutchings et al. 2019). Although experts are well-informed about the origins of this crisis, it is seldom communicated to the broader public.

The discovery of penicillin by Alexander Fleming in 1928 was accompanied by his own forewarning regarding the imminent emergence of bacterial resistance to this "miracle drug" (Khardori et al. 2020; Tan and Tatsumura 2015). In the over 70 years since the introduction of penicillin, the overuse and misuse of antibiotics, coupled with their widespread application in agriculture for prophylactic purposes and growth enhancement, have exacerbated the issue of MDR bacterial infections (Santesmases and Gradmann 2011). The CDC reports that over 70% of antibiotics administered in the U.S. are utilized in agricultural settings (Abadi et al. 2019; Michael et al. 2014). Antibiotic stewardship and surveillance initiatives have shown limited efficacy in combating the MDR crisis (Romo and Quiroz 2019). Recently, both the CDC and the White House have articulated explicit objectives for addressing antibiotic resistance, aiming to mitigate the proliferation of MDR bacteria through international collaboration by 2020 (Centers for Disease Control, 2020; Obama White House Archives 2015). Unfortunately, this Executive Order signed by President Barack Obama (#13676) remains unaddressed, allowing MDR bacterial infections to escalate and become increasingly prevalent (CDC 2020; Floris et al. 2020). Should no new effective antibiotics be developed and approved for clinical application by 2050, it is projected that MDR bacteria will result in more deaths globally than diabetes and cancer combined (Small World Initiative 2020), underscoring the urgent need for immediate action to tackle this challenge.

In contemporary society, the medical field is confronted with numerous challenges that outpace its advancements, raising significant concerns for medical science and society at large. Novel diseases are crossing international borders at alarming rates, bringing pathogens that were once geographically

confined to new populations with vulnerable individuals. Additionally, diseases previously deemed contained or extinct are re-emerging with new resistances to conventional treatment methods, necessitating unprecedented measures. Furthermore, diseases transmitted by infected living vectors, such as insects and rodents, pose increasing threats due to the emergence of pesticide-resistant carriers. These issues are merely a fraction of the myriad challenges confronting modern medicine.

One of the foremost challenges to contemporary medicine is the rising resistance of prevalent bacterial pathogens to antibiotics. According to the Centers for Disease Control and Prevention (CDC), nearly 3 million individuals in the United States become infected each year with various strains of antibiotic-resistant bacteria or fungi, resulting in over 35,000 deaths (About Antibiotic Resistance 2020; Biggest Threats and Data 2020). Among the most alarming drug-resistant bacterial infections are MRSA (methicillin-resistant Staphylococcus aureus), VRSA (vancomycin-resistant S. aureus), VRE (vancomycin-resistant Enterococcus), drug-resistant Salmonella and Campylobacter infections, and multi-drug-resistant Mycobacterium tuberculosis infections, among others (Biggest Threats and Data 2020; World Health Organization 2020; Frieri et al. 2017; Zaman et al. 2017). The overuse of antibiotics for these infections, as well as inappropriate prescribing of antibiotics for conditions they are not designed to treat—such as viral infections—has led to widespread resistance among various bacterial species to numerous commonly used antibiotics. This misuse has also resulted in numerous instances of opportunistic or nosocomial infections in patients worldwide (D'Costa et al. 2011; Frieri et al. 2017; Davies and Davies 2010; Munita and Arias 2016; Chellat et al. 2016; Zaman et al. 2017). Many of these infections present significant treatment challenges, particularly if the bacterial strains involved exhibit multiple resistance mechanisms (Frieri et al. 2017; Munita and Arias 2016). The rapid spread of resistance is facilitated by the swift replication cycles of bacteria and the transfer of resistance genes through conjugation, allowing for the transmission of various natural and plasmid-mediated resistances (Davies and Davies 2010; Chellat et al. 2016).

Davies and Davies (2010) report that there are likely over 20,000 known resistance genes encompassing more than 400 general types, based on the extensive library of available bacterial genome sequences, with many more yet to be discovered. They caution that the world may regress to a pre-antibiotic era where these "miracle drugs" are rendered largely ineffective, emphasizing the necessity for effective solutions to this pressing issue. Moreover, Munita and Arias (2016) predict that antibiotic resistance could lead to the premature loss of 300 million lives globally and impose a staggering economic burden of approximately 100 trillion U.S. dollars by the year 2050. The prevailing objective of many medical researchers and healthcare professionals is to devise strategies to confront this global resistance crisis. These strategies include curtailing the excessive and unwarranted use of antibiotics, restricting the irresponsible sale of these medications, especially in developing nations, and educating the public on the responsible use of antibiotics (Chellat et al. 2016; Santesmases and Gradmann 2011). Additionally, there is a pressing need for the development of novel antibiotic compounds and classes, as well as the chemical modification of existing ones.

Brief History of Antibiotic Resistance

The narrative of antibiotics traces back to the late 19th century, when French physician Ernest Duchesne observed that certain fungal molds, particularly Penicillium, could inhibit bacterial proliferation (Ramalingam 2015). Regrettably, Dr. Duchesne passed away in the early 1920s without elucidating the mechanisms by which Penicillium and similar molds combat bacteria. Subsequently, in 1928, Sir Alexander Fleming, a Scottish physician and researcher, identified penicillin after noticing the growth of Penicillium mold on a culture plate of Staphylococcus bacteria, where the mold effectively inhibited surrounding bacterial growth (Davies and Davies 2010; Zaman et al. 2017; Santesmases and Gradmann 2011; Ramalingam 2015). Building on his earlier discovery of the antibacterial enzyme lysozyme in 1923, which is naturally present in human tears and integral to the immune response, Fleming hypothesized that Penicillium produced a similar compound. Although he successfully extracted this substance, he was unable to purify it, halting his research until it was finally purified and utilized in clinical trials approximately a decade later. In the early 1940s, scientists Howard Walter Florey and Ernst Boris Chain successfully purified Fleming's substance, conducting laboratory experiments that demonstrated its efficacy against bacterial infections (Santesmases and Gradmann 2011; Ramalingam 2015; Bjorkman and Phillips-Howard 1991). By 1943, penicillin G entered mass production and medical application, proving to be remarkably effective in treating a variety of bacterial infections, especially among soldiers during World War II (Davies and Davies 2010; Zaman et al. 2017; Santesmases and Gradmann 2011; Ramalingam 2015; Bjorkman and Phillips-Howard 1991).

In the interval between Fleming’s initial discovery and the purification efforts by Florey and Chain, Gerhard Domagk, a German pathologist and bacteriologist, discovered and developed a class of synthetic compounds known as sulfonamides, commonly referred to as “sulfa drugs” throughout the 20th century (Ramalingam 2015; Bjorkman and Phillips-Howard 1991; Lesch 2007). However, these antibiotics were eventually relegated to secondary status following the advent of penicillin and other antibiotics in the 1940s, especially after it became evident that they could induce severe side effects, such as blood dyscrasias and liver disorders, leading to their discontinuation. Nevertheless, their introduction catalyzed a revolution in antibiotic discovery and production in subsequent decades.

From the mid-1940s to the late 1950s, a plethora of new antibiotics derived from microbial sources emerged, following the discoveries of penicillin and sulfonamides. These included streptomycin, erythromycin, cephalosporins, bacitracin, chloramphenicol, polymyxin, tetracycline, aminoglycosides, macrolides, vancomycin, and neomycin (Zaman et al. 2017; Ramalingam 2015). These compounds effectively treated conditions such as bacterial pneumonia, syphilis, and tuberculosis (Ramalingam 2015). However, several of these antibiotics, like neomycin, proved too toxic for human use, necessitating a reduction in their clinical application. This prompted the search for new semi-synthetic and fully synthetic antibiotics with enhanced activity. In 1960, the first semi-synthetic antibiotic, methicillin, was developed from penicillin, followed by

the production of nalidixic acid in 1962. These and other contemporaneous antibiotics were notably effective against various bacterial strains, including Staphylococcus and Escherichia coli. The 1960s also saw the emergence of first-generation cephalosporins, eventually leading to the development of second- and third-generation cephalosporins and carbapenems in subsequent decades (Ramalingam 2015). While the period from the 1950s to the 1970s is often dubbed the "golden age" of antibiotic discovery, a significant decline in novel antibiotic development has been observed since the late 1980s, culminating in what has been referred to as a discovery void, even as drug-resistant infections began to emerge prior to this era.

Today, research into new antibiotic compounds that target drug-resistant bacteria is more prevalent than ever. The British Medical Journal highlights the pressing issue of insufficient novel antibiotics to combat drug-resistant infections, noting that research funding for critical pathogens like tuberculosis and various Gram-negative infections remains inadequate (Kmietowicz 2017). Despite this, numerous research initiatives are underway to explore and develop novel compounds for treating a range of infections. Research involving fungi has shown promise in this domain, with He et al. studying naphtho-γ-pyrones derived from fungi (He et al. 2016). These fungal polyketides exhibit significant antimicrobial properties against a variety of pathogens, including S. aureus and M. tuberculosis. Their investigation focused on eight specific compounds, with findings indicating that fonsecinones A and C, as well as aurasperones A and E, demonstrated potential antimicrobial activity against MRSA and E. coli, with fonsecinone A exhibiting the highest efficacy (He et al. 2016).

Additionally, Silber et al. emphasized the vast potential for antibiotic discovery from marine fungi (Silber et al. 2016). Their review of biotechnological advancements related to marine fungi details numerous candidate compounds with notable antimicrobial activity against ESKAPE pathogens, such as ascosetin from Halichondria panicea, effective against MRSA, and various cephalosporins derived from Aspergillus chrysogenum (Silber et al. 2016). They also explore diverse biotechnological methods for mass-producing these compounds, including natural fermentation and bioconversion techniques (Silber et al. 2016). In some cases, antibiotic production involves multi-species colonies, as demonstrated in Stierle et al.'s research, which identified a new series of macrolide antibiotics termed berkeleyactones (Stierle et al. 2017). These 16-membered-ring antibiotics were produced through a carefully timed coculture fermentation process involving Penicillium fuscum and P. camembertii/clavigerum, both extremophilic fungi sourced from the acidic waters of Berkeley Pit Lake (Stierle et al. 2017). The study revealed that while axenic cultures yielded no useful compounds, coculturing resulted in the production of berkeleyactones and other secondary metabolites. Among the eight berkeleyactones tested, berkeleyactone A exhibited the most significant antibiotic activity against several pathogens, including MRSA, with a minimum inhibitory concentration of 1–2 μg/mL (Stierle et al. 2017). Furthermore, this compound likely possesses a novel mechanism of action, distinct from other macrolides, which remains to be characterized (Stierle et al. 2017).

Potential strategies for reintroducing older antibiotic classes into clinical use have emerged. Shang et al. (2016) conducted a study on the biotransformation of tetracycline antibiotics through various fungal species, highlighting the remarkable resilience of viridicatumtoxins. These toxins, sourced from fungi such as *Penicillium viridicatum* and *P. aethiopicum*, demonstrated significant resistance to fungal biotransformation processes in Shang et al.'s experiments. Notably, viridicatumtoxin B exhibited a minimum inhibitory concentration (MIC) of 40 nanomoles (nM) against vancomycin-resistant Enterococci (Shang et al. 2016). The researchers concluded that certain tetracyclines may possess a pronounced ability to withstand enzymatic degradation, thereby making them valuable against diverse bacterial and fungal targets and potentially guiding the development of new tetracycline antibiotics with similar resistance profiles (Shang et al. 2016).

Additional research emphasizes the potential for discovering novel compounds from natural sources (Moloney 2016; Hug et al. 2018; Landwehr et al. 2016). This body of work presents various examples, including teixobactin (a bacterially produced compound effective against a wide range of organisms, especially Gram-positive bacteria), ulleungamides, salinamide F (active against both Gram-positive and Gram-negative bacteria), copsin (isolated from a co-cultivated fungal source), cystobactamids, hymenosetin, kibdelomycin, and hunanamycin (derived from the marine bacterium *Bacillus hunanensis*), along with simocyclinones and others. Significant untapped potential for antibiotic discovery persists within the Actinobacteria phylum and Myxobacteria group, particularly in underexplored environments such as marine, tropical, semi-arid, and polar regions (Hug et al. 2018; Landwehr et al. 2016). Serpi, Ferrari, and Pertusati (2016) reviewed the potential application of nucleosides and their analogs as antibiotic agents against bacterial and fungal infections. Their article highlights that nucleosides and nucleoside analogs have previously shown moderate to strong antibiotic activity and are already integral to antiviral and anticancer treatments, suggesting their antibiotic applications could be expanded with further investigation into their mechanisms and chemical interactions (Serpi et al. 2016). Compounds derived from nucleosides have been identified as targeting essential biochemical processes in bacteria and fungi, such as nucleoside metabolism and the biosynthesis of cell walls, nucleic acids, and proteins (Serpi et al. 2016). Additionally, this study notes that nucleoside analogs target various other cellular processes within these organisms, albeit less understood, indicating the potential for discovering new chemical compounds and mechanisms with antibiotic capabilities (Serpi et al. 2016).

Several studies have identified innovative treatment options for specific bacterial targets. For instance, Bassères et al. (2016) list potential novel pharmaceuticals that could be effective against *Clostridioides difficile* infections, including surotomycin (a semisynthetic lipopeptide), ridinilazole (a narrow-spectrum antibiotic targeting *C. difficile* and other related species), ramoplanin (a glycolipodepsipeptide), and cadazolid (a hybrid fluoroquinolone/oxazolidinone antibiotic). Furthermore, Koulenti et al. (2019) identify various novel compounds that may be employed for treating primarily Gram-positive bacterial infections such as *S. aureus* and *Streptococcus pneumoniae*, including new cephalosporins (ceftaroline and ceftobiprole), glycopeptides (telavancin, dalbavancin, and

oritavancin), the oxazolidinone tedizolid phosphate, quinolones (besifloxacin, delafloxacin, and ozenoxacin), and the tetracycline omadacycline.
Specifically regarding *S. aureus*, one of the most prevalent and challenging drug-resistant pathogens in human disease, Mohammad et al. synthesized two novel thiazole compounds that demonstrated significant antimicrobial efficacy against multi-drug resistant *S. aureus*, including MRSA and VRSA strains, with MIC values of 1.38 μg/mL for the first compound and 1.40 μg/mL for the second (Mohammad et al. 2015). Notably, the second compound, a derivative of the first, successfully re-sensitized VRSA to vancomycin's effects. The researchers concluded that both compounds, either independently or in combination with vancomycin, could effectively combat multi-drug resistant *Staphylococcus* species and disrupt mature biofilms formed by these bacteria.

To comprehensively address antibiotic resistance, it is crucial to explore not only the history of antibiotic development and medical usage but also the historical context of resistance itself. As previously mentioned, antibiotic resistance is not a novel issue, with reports dating back to the so-called golden age of antibiotic discovery (Davies and Davies 2010; Zaman et al. 2017; Ramalingam 2015). Evidence suggests that the history of antibiotic resistance may be even more extensive than initially believed (D'Costa et al. 2011). Therefore, understanding the origins of this challenge is vital for guiding the future development of antibiotic compounds to minimize or eliminate resistance issues moving forward. Moreover, this knowledge is essential to prevent the repetition of past mistakes.

Development of Antibiotics and Resistance

Contrary to what might be expected, evidence suggests that antibiotic resistance in microorganisms predates contemporary medical history, indicating a process with a significant evolutionary background not limited to human documentation. D'Costa et al. (2011), utilizing paleogenetic techniques such as polymerase chain reaction (PCR) and genomic sequencing, propose that the origins of antibiotic resistance could date back as far as 40 million years or potentially extend to 2 billion years. Their research, primarily focused on Pleistocene megafauna and the Actinobacteria family, demonstrates the prevalence of antibiotic resistance genes long before modern times. The findings imply that antibiotic resistance has been a naturally occurring phenomenon throughout history, suggesting that new antibiotics often select for existing resistances, which should inform both current and future antibiotic development and application.

The contemporary timeline of antibiotic resistance began around the introduction of sulfonamide antibiotics in the 1930s. By the late 1930s, shortly after the widespread adoption of sulfonamides in 1937, resistant bacterial strains started to appear in clinical settings (Zaman et al. 2017). The subsequent introduction of penicillin and other antibiotics in the early 1940s also saw the emergence of resistance among various bacterial strains (Davies and Davies 2010). Notably, prior to penicillin's public use, during the purification and laboratory studies conducted by Florey and Chain, bacterial penicillinases were identified by members of the discovery team. Once penicillin became widely used, resistant bacterial strains capable of deactivating the antibiotic proliferated, necessitating the chemical modification of penicillin to thwart cleavage by these enzymes.

Ironically, Alexander Fleming was the first to caution against the risk of bacterial resistance to penicillin resulting from incomplete treatments or insufficient dosages (Zaman et al. 2017). Shortly after penicillin's introduction, in 1944, the antibiotic streptomycin, produced from microbes, began being used to treat tuberculosis infections. However, complications arose as resistant strains of the infection began to survive therapeutic concentrations during treatment. Many subsequent antibiotics developed for tuberculosis treatment exhibited similar patterns of resistance.

In the 1950s, the phenomenon of genetic transfer of antibiotic resistance via bacterial conjugation was identified in Japan, a revelation initially met with skepticism in the West. This finding underscored that resistance genes could be rapidly disseminated within bacterial populations and even exchanged between closely related genera and species. During the same decade, resistant strains of Staphylococcus aureus emerged within six years of the introduction of aminoglycosides (Zaman et al. 2017; Ramalingam 2015). By the early 1960s, methicillin was introduced as the first semisynthetic penicillinase-resistant antibiotic to target penicillinase-producing S. aureus strains, but resistance to methicillin was soon reported after its approval. In the 1980s, fluoroquinolones were primarily utilized to treat Gram-negative infections, but resistance soon became apparent with these drugs as well, particularly through stepwise mutations in methicillin-resistant strains. Clinical isolates of vancomycin-resistant S. aureus (VRSA) were identified in 2002, 44 years after the antibiotic's introduction in 1958.

Bacteria employ numerous biological and biochemical strategies to evade or resist antibiotic effects. Some prominent mechanisms include the chemical alteration of antibiotics, often achieved through enzymes that fundamentally modify the drug. For instance, steric hindrance via acetylation, adenylation, or phosphorylation can render antibiotics less effective (Munita and Arias 2016; Zaman et al. 2017). Aminoglycosides can be modified by bacterial aminoglycoside modifying enzymes (AMEs), which covalently alter the hydroxyl or amino groups of the antibiotic. Similarly, chloramphenicol, which inhibits protein synthesis by targeting the peptidyl transfer center of the bacterial 50S ribosomal subunit, can be chemically modified by acetyltransferases known as chloramphenicol acetyltransferases (CATs).

Another significant resistance mechanism involves β-lactamases, which degrade β-lactam antibiotics. S. aureus is a common drug-resistant bacterium that employs β-lactamases (Munita and Arias 2016). A critical issue with β-lactamases is their rapid evolution, often rendering new β-lactam antibiotics ineffective shortly after introduction. Current estimates indicate that over 1000 β-lactamases are known, with likely many more to be identified through ongoing research. Extended spectrum β-lactamases (ESBLs) can hydrolyze a range of antibiotics, including penicillin and its derivatives, third-generation cephalosporins, and monobactams, but exhibit minimal to no activity against cephamycins and carbapenems.

Bacteria also resist antibiotics through mechanisms involving decreased permeability, efflux, and alterations to target sites. Reduced membrane

permeability is particularly problematic for Gram-negative bacteria, which possess multi-layered membranes that hinder the entry of certain antibiotics, such as β-lactams, due to variations in the expression of membrane molecules like porins. Efflux pumps are bacterial membrane systems that expel antibiotics from the cell before they can exert their effects, often exhibiting substrate specificity for certain antibiotic classes, including macrolides and β-lactams. Additionally, bacteria may alter their antibiotic target sites through various mechanisms, including target protection, non-genetic modifications, mutations, enzymatic changes, or complete bypassing of the target site (Munita and Arias 2016; Zaman et al. 2017).

One of the most enduring and challenging forms of bacterial resistance is the formation of biofilms. Biofilms consist of clusters of microorganisms closely associated and often attached to inert surfaces, embedded in a resilient extracellular matrix composed of polysaccharides, proteins, and nucleic acids (Frieri et al. 2017; Davies and Davies 2010). Several drug-resistant bacterial species, including Staphylococcus aureus and Pseudomonas aeruginosa, can form biofilms, which provide both physical and chemical defenses against many standard antibiotics, complicating treatment and posing significant risks to patients affected by these particularly resistant strains. Once biofilms adhere to surfaces, they are notoriously difficult to eradicate. Biofilms facilitate bacterial colonization on medical devices, surgical implants, commonly used surfaces, and human tissues, such as skin or internal organs.

ESKAPE Pathogens

The challenge of antibiotic resistance involves several high-profile bacterial targets, particularly those classified within the ESKAPE group. This section focuses on these concerning pathogens, all of which will be integral to the experimental methods outlined later in this paper. The acronym ESKAPE is derived from the initial letters of the genus names of each bacterium in this category: Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and various species of Enterobacter. Detailed discussions of each species follow.

The first member of the ESKAPE group, *Enterococcus faecium*, is a Gram-positive, spherical (coccus) bacterium. *E. faecium*, alongside its closely related counterpart *Enterococcus faecalis* and other Enterococcus species, is typically found as a benign component of the gastrointestinal microbiome in both humans and non-human animals, as well as in the female reproductive tract and in environmental contexts like water and soil (Pathogen Page 2020; Willems et al. 2005; O'Driscoll and Crank 2015; Vancomycin Resistant Enterococci 2020). However, under certain conditions, these bacteria can act as opportunistic pathogens. Notably, vancomycin-resistant strains of *Enterococcus* are particularly concerning; in 2017, the CDC estimated nearly 55,000 drug-resistant bacterial infections due to vancomycin-resistant *Enterococcus* (VRE), with about 10% of these cases resulting in death. The CDC also reported that around 30% of all nosocomial enterococcal infections are vancomycin-resistant, highlighting an alarming trend of increasing resistance among various *Enterococcus* species, which poses significant challenges for future treatment. Furthermore, concerns arise regarding VRE

acting as reservoirs for resistance genes transferable to other bacterial pathogens. For instance, the first case of vancomycin-resistant Staphylococcus aureus (VRSA) reported in 2002 was linked to the transfer of the vanA resistance gene from a vancomycin-resistant *Enterococcus* strain (Frieri et al. 2017; Willems et al. 2005; O'Driscoll and Crank 2015).

In addition to their ability to utilize and transfer resistance genes, *E. faecium* and related species possess various mechanisms enabling them to evade or resist conventional antibiotics (O'Driscoll and Crank 2015; Heikens et al. 2007). Beyond vancomycin, *E. faecium* demonstrates resistance to several antibiotic classes, including β-lactams, aminoglycosides, and glycopeptides, due to factors like penicillin-binding proteins (PBPs), aminoglycoside-modifying enzymes, and the elimination of high-affinity D-alanine precursors that glycopeptide antibiotics typically target. Additionally, *E. faecium* exhibits remarkable survivability on various surfaces, persisting for up to one hour on human skin and up to four months on inorganic surfaces. The presence of surface proteins facilitates adherence to multiple surfaces, enabling biofilm formation, which complicates antibiotic treatment (Heikens et al. 2007).

The aforementioned traits allow these bacteria to colonize diverse environments, including healthcare-related surfaces such as countertops, surgical trays, medical equipment, and various surgical implants like joint replacements, heart valves, cardiac stents, organ transplants, and catheters (Vancomycin Resistant Enterococci 2020; Willems et al. 2005; O'Driscoll and Crank 2015; VRE Pathogen Page 2020; Heikens et al. 2007). According to the CDC, in solid organ transplant units, vancomycin-resistant *E. faecium* is the leading cause of nosocomial bloodstream infections.

E. faecium is also a frequent cause of several infections, including bacterial endocarditis, intra-abdominal and pelvic infections, urinary tract infections (UTIs), rare central nervous system infections such as meningitis, and skin infections like abscesses. The most effective preventive measure against such infections is stringent hygiene and regular disinfection of surfaces that may come into contact with VRE. Evidence suggests that employing synergistic treatments involving multiple antibiotics to counteract specific resistance traits of *E. faecium* could be a promising strategy for managing infections. Importantly, healthy individuals may harbor VRE in their gastrointestinal or reproductive tracts without experiencing infection, as these bacteria are a natural part of the microbiota and typically pose minimal risk.

Another well-known member of the ESKAPE group is *Staphylococcus aureus*. This Gram-positive, spherical bacterium is commonly found as a commensal organism in the nasal passages of approximately 30% of the population and is a regular component of the skin microbiome. Although *S. aureus* is generally associated with minor skin infections, the emergence of antibiotic-resistant strains has escalated concerns regarding its pathogenic potential (Frieri et al. 2017; Davies and Davies 2010; Zaman et al. 2017). Strains exhibiting high resistance levels, particularly methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *S. aureus* (VRSA), have become significant nosocomial threats (MRSA 2020). Following the introduction of penicillin and its derivatives, such as

methicillin, *S. aureus* quickly developed substantial resistance due to the production of penicillinases and other defense mechanisms. Indeed, resistant strains of *S. aureus* emerged just three years after methicillin's introduction in the early 1960s.

According to the CDC, despite a gradual decline in reported MRSA cases, over 300,000 MRSA infections were recorded in 2017, resulting in approximately 10,600 fatalities (Dinges et al. 2000). *S. aureus* is an opportunistic pathogen equipped with various mechanisms to initiate infection and persist within human hosts. It produces numerous enzymes, toxins, adhesins, and other molecules facilitating its pathogenicity (Frieri et al. 2017; Dinges et al. 2000; Chambers 2001). A significant group of these toxins, known as pyrogenic toxin superantigens (PTSAgs), comprises a variety of exotoxins produced by both *S. aureus* and *Streptococcus pyogenes*. Notably, the TSST-1 exotoxin, produced by approximately 25% of *S. aureus* strains, plays a crucial role in the symptoms associated with toxic shock syndrome induced by this bacterium.

Staphylococcus aureus is notably adept at forming biofilms, which complicates treatment efforts, particularly with drug-resistant strains like MRSA and VRSA. Beyond skin and soft tissue infections, S. aureus, including its resistant variants, is associated with various serious conditions such as toxic shock syndrome, bacteremia, sepsis, respiratory infections (including pneumonia), osteomyelitis, and endocarditis (Frieri et al. 2017; Davies and Davies 2010; Chambers 2001; MRSA Pathogen Page 2020). MRSA primarily spreads through direct skin contact and the sharing of personal hygiene items, allowing for rapid community transmission (MRSA 2020). Hence, maintaining good hygiene practices, avoiding the sharing of personal items, and ensuring that wounds are kept clean and covered are crucial preventive measures.

Klebsiella pneumoniae is a Gram-negative, non-motile, lactose-fermenting bacillus known for its role in pneumonia, especially in hospital settings. Although it may exist harmlessly in the skin, nasopharynx, and gastrointestinal tract, K. pneumoniae is an opportunistic pathogen frequently implicated in infections such as pneumonia, urinary tract infections, and sepsis (Vuotto et al. 2014; Ashurst and Dawson 2020). Characteristically, K. pneumoniae infections lead to significant tissue inflammation, producing thick, jelly-like sputum that distinguishes it from other bacterial pneumonias (Nordmann et al. 2009). Alarmingly, K. pneumoniae accounted for approximately 80% of all carbapenem-resistant Enterobacteriaceae infections in 2013 (Ashurst and Dawson 2020), with an estimated 12% of hospital-acquired pneumonia cases worldwide attributed to it.

Patients on ventilators, as well as those with chronic alcoholism and septicemia, face heightened mortality risks from K. pneumoniae infections, particularly those caused by drug-resistant strains that produce Klebsiella pneumoniae carbapenemases (KPCs) (Ashurst and Dawson 2020). These enzymes primarily target carbapenems and can hydrolyze various other antibiotics. Treatment options for KPC-producing infections include colistin, tigecycline, and aminoglycosides, though some strains exhibit resistance even to these drugs. Combining remaining treatment options may enhance survival for patients

suffering from K. pneumoniae-mediated bacteremia (Munoz-Price et al. 2009). The bacterium's ability to form thick biofilms further complicates treatment and increases the risk of recurrent infections (Anderl et al. 2000; Vuotto et al. 2014). To curtail its spread in healthcare settings, strict infection control measures, including hygiene practices and disinfection of medical equipment, are essential.

Acinetobacter baumannii is among the most concerning members of the ESKAPE pathogen group, characterized by its extensive antibiotic resistance mechanisms, which complicate treatment (Davies and Davies 2010; Acinetobacter Pathogen Page 2020). The CDC ranks it as an urgent threat, having affected approximately 8,500 patients in 2017, resulting in about 700 deaths (Acinetobacter Pathogen Page 2020; Acinetobacter CDC 2020). A. baumannii is associated with various infections, including hospital-acquired pneumonia and skin infections, and is notorious for its resistance, with some strains being pan-drug resistant (Howard et al. 2012). This pathogen thrives in healthcare environments, exhibiting a remarkable capacity for survival in diverse conditions (Peleg et al. 2008).

The bacterium employs multiple resistance strategies, such as producing β-lactamases and modifying outer membrane proteins, leading to decreased antibiotic susceptibility (Peleg et al. 2008; Dijkshoorn et al. 2007). Alarmingly, carbapenem-resistant strains can exchange resistance genes with other bacteria, exacerbating the challenge of treating infections. Preventive measures primarily hinge on rigorous hygiene and disinfection protocols to limit transmission, especially in healthcare settings. Pseudomonas aeruginosa, another Gram-negative bacillus, is typically a benign environmental organism, yet it poses significant risks for immunocompromised patients and those with chronic lung diseases (Pseudomonas CDC 2020). It is responsible for 10-15% of nosocomial infections globally and is a common cause of ventilator-associated pneumonia and surgical site infections (Aloush et al. 2006; Strateva and Yordanov 2009). Multi-drug resistant strains, including some that are carbapenem-resistant, have emerged, complicating treatment options (MDR Pseudomonas 2020; Pseudomonas CDC 2020). The resistance mechanisms in P. aeruginosa include β-lactamases and altered expression of outer membrane proteins, allowing it to evade many common antibiotics (Poole 2011; Sadikot et al. 2005). Interestingly, targeting iron ion access could mitigate biofilm formation, potentially enhancing treatment effectiveness (Banin et al. 2005). Preventive measures in healthcare settings focus on maintaining stringent hygiene practices to protect vulnerable patients (Pseudomonas CDC 2020).

Finally, Enterobacter species, which are Gram-negative bacilli, also exhibit significant antibiotic resistance. These bacteria are typically found in the environment and as part of the gut microbiota but can lead to severe healthcare-associated infections, particularly in drug-resistant forms (Davin-Regli and Pagès 2015; Mezzatesta et al. 2012). Extended-spectrum β-lactamase (ESBL)-producing Enterobacter strains are particularly concerning, responsible for numerous drug-resistant infections (ESBL Pathogen Page 2020; CRE CDC 2020). Treatment usually involves carbapenem antibiotics, but resistance to these drugs poses significant challenges. Some recent studies suggest fosfomycin may be effective against Enterobacter, alongside combination therapies involving meropenem and vaborbactam for combating carbapenem-resistant infections (Falagas et al. 2010;

Castanheira et al. 2017). As these bacteria continue to evolve, understanding their mechanisms and implementing strict infection control measures will be essential to mitigate their impact in healthcare settings.

Conclusion

Antibiotic resistance remains one of the most significant challenges facing healthcare today. The projections that MDR infections could result in 10 million deaths annually by 2050 underscore the urgency of addressing this issue. The failure to develop new antibiotics over the past few decades has created a void that threatens to undermine decades of medical progress. This review has highlighted the multifaceted nature of antibiotic resistance, exploring historical patterns, contemporary challenges, and emerging solutions. Education and awareness among healthcare staff are paramount. Many practitioners may not fully grasp the extent of the crisis or the mechanisms behind resistance. Increasing knowledge about the inappropriate use of antibiotics, particularly in non-bacterial infections, can lead to more prudent prescribing practices. Furthermore, the agricultural sector's role in antibiotic misuse must be scrutinized, as over 70% of antibiotics in the U.S. are used in agriculture. This misuse not only affects animal health but also has far-reaching implications for human health, as antibiotic residues can enter the food chain. On the research front, there is hope. The exploration of novel compounds from underutilized sources, such as marine fungi and Actinobacteria, shows promise. Innovations like coculture fermentation have led to the discovery of new antibiotics with mechanisms of action distinct from existing drugs, which is critical for overcoming resistance. Collaborations between academia, industry, and government entities are essential to foster an environment conducive to antibiotic discovery and development. Additionally, reinforcing antibiotic stewardship initiatives is crucial. Healthcare facilities should implement strict protocols for prescribing antibiotics and monitor usage patterns to reduce unnecessary prescriptions. Public health campaigns aimed at educating the public on the responsible use of antibiotics can further mitigate the problem. In conclusion, while the challenges posed by antibiotic resistance are daunting, a multifaceted approach involving education, research, and stewardship can help to combat this growing crisis. The integration of these strategies into healthcare practice will be essential for safeguarding the effectiveness of antibiotics for future generations.

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فهم مقاومة المضادات الحيوية: التحديات والحلول ـ مقالة مراجعة لموظفي الرعاية الصحية

الملخص:
الخلفية :تشكل مقاومة المضادات الحيوية (ABR) تهديدًا حرجًا للصحة العالمية، حيث تشير التوقعات إلى أنه بحلول عام 2050، يمكن أن تؤدي العدوى المقاومة لأدوية متعددة (MDR) إلى حوالي 10 ملايين وفاة سنويًا، متجاوزة بذلك الوفيات الناجمة عن السرطان وأمراض القلب والأوعية الدموية. لقد ساهم الإفراط في استخدام المضادات الحيوية وسوء استخدامها، لا سيما في البيئات الزراعية، في تفاقم هذه المشكلة.
الهدف :تهدف هذه المراجعة إلى تزويد موظفي الرعاية الصحية بفهم للتحديات التي تطرحها مقاومة المضادات الحيوية واستكشاف الحلول المحتملة.
الطرق :تم إجراء مراجعة شاملة للأدبيات، تحليل البيانات التاريخية والمعاصرة حول اكتشاف المضادات الحيوية، وآليات المقاومة، والمبادرات البحثية الحالية التي تهدف إلى معالجة مقاومة المضادات الحيوية.
النتائج :تشير النتائج الرئيسية إلى أن الانخفاض في تطوير المضادات الحيوية الجديدة منذ أواخر الثمانينيات، بالإضافة إلى الانتشار السريع لجينات المقاومة، قد خلق حاجة ملحة لاستراتيجيات علاجية جديدة. تسلط الأبحاث الحديثة الضوء على المركبات الواعدة المستمدة من المصادر الطبيعية، بما في ذلك الفطريات البحرية والبكتيريا الشرطية، التي تظهر إمكانات ضد مسببات الأمراض المقاومة لأدوية متعددة.
الخاتمة :هناك حاجة إلى اتخاذ إجراءات فورية لمكافحة مقاومة المضادات الحيوية، بما في ذلك تحسين إدارة المضادات الحيوية، وتوعية الجمهور، وزيادة التمويل للبحث في المضادات الحيوية الجديدة. تعتبر الجهود التعاونية بين محترفي الرعاية الصحية والباحثين وصانعي السياسات ضرورية لمعالجة هذه الأزمة المتصاعدة.
الكلمات المفتاحية :مقاومة المضادات الحيوية، البكتيريا المقاومة لأدوية متعددة، موظفو الرعاية الصحية، إدارة المضادات الحيوية، مضادات حيوية جديدة، الصحة العالمية.