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Antimicrobial Resistance in Hospital Infections: Identification of Patterns, Risk Factors, and Management Strategies

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Abstract

Antimicrobial resistance (AMR) has emerged as a global health crisis, posing a severe threat to our ability to combat infectious diseases effectively. The misuse and overuse of antibiotics have accelerated the development of AMR, leading to thousands of deaths worldwide. Hospitals, especially intensive care units, have become hotspots for the emergence and spread of antibiotic-resistant pathogens. This article delves into the complex dynamics of AMR, emphasizing its global dimensions, resistance mechanisms, associated risk factors, management and prevention strategies, and emerging technologies for future directions. Microorganisms can develop resistance through efflux pumps, interference with antibiotic target sites, and bacterial enzyme inactivation.

Mobile genetic elements often facilitate these mechanisms, allowing resistance genes to spread rapidly among bacterial species. Hospitals play a significant role in the AMR crisis due to factors like high antibiotic use, indwelling devices, and the vulnerability of patients. Various risk factors, including immunosuppression, invasive procedures, and extensive antimicrobial use, contribute to the development and spread of AMR in healthcare settings. Management and prevention strategies are essential to tackle AMR. New antibiotics are needed to combat resistant pathogens, and research highlights the efficacy of combinations like ceftaroline and daptomycin for MRSA treatment and novel antibiotics for gram-negative pathogens. Preventive measures encompass awareness campaigns, surveillance, infection control, and optimized antimicrobial use.

Targeted hygiene practices, focused on critical moments, can break the chain of infection in everyday settings. Antibiotic use in animals also contributes to AMR, necessitating regulations and monitoring. Shortening antibiotic courses, communication skills training for clinicians, rapid diagnostic tests, and active monitoring are additional strategies to optimize antibiotic use. The battle against AMR is multifaceted, involving a global effort to understand, manage, and prevent resistance. With the development of new technologies and a commitment to responsible antibiotic use, there is hope for a future where effective treatment of infectious diseases remains attainable.

Keywords: Antimicrobial resistance; Antibiotics; Multidrug resistant pathogens; Resistance mechanisms; Hospital-acquired infections; MRSA; Responsible antimicrobial use

Abbreviations: AMR: Antimicrobial Resistance; CDC: Centers for Disease Control and Prevention; ESBL: Extended-Spectrum Beta-Lactamase; GAP: Global Action Plan; HIV: Human Immunodeficiency Virus; IDSA: Infectious Disease Society of America; MDR: Multidrug-Resistant; MIC: Minimal Inhibitory Concentration; MRSA: Methicillin-Resistant Staphylococcus Aureus; NAAT: Nucleic Acid Amplification Technologist; SELEX: Systematic Evolution of Ligands by Exponential Enrichment; VRE: Vancomycin-Resistant Enterococci; VRSA: Vancomycin-Resistant Staphylococcus Aureus; WHO: World Health Organization

Introduction

Antimicrobial resistance (AMR) has evolved into a formidable global health crisis, posing a profound threat to our ability to combat infectious diseases effectively. As the effectiveness of existing antibiotics crumbles, we find ourselves in a race against

time to develop innovative strategies, treatments, and policies to address this escalating challenge. The rise of multidrug-resistant pathogens and an arsenal of new antibiotics is a recipe for disaster. Over the past decade, scientists, clinicians, and public health experts have joined forces to unravel the intricate resistance mechanisms, paving the way for breakthrough discoveries in our understanding of microbial adaptation.

The global dimension of AMR is emphasized as we analyze the dynamics of resistance dissemination and the role of international collaborations in surveillance and containment efforts. We consider the impact of antimicrobial stewardship programs and the evolving regulatory landscape in promoting responsible antimicrobial use. As we embark on this exploration of the latest AMR research, it is evident that our collective commitment to understanding, addressing, and mitigating antimicrobial resistance is more crucial than ever. This review aims to provide a comprehensive and up-to-date overview of the multifaceted battle against AMR, inspiring renewed dedication to a future where effective treatment of infectious diseases remains within our grasp [1-3].

Antimicrobial Resistance in Hospitals

Antimicrobial resistance (AMR) is a natural phenomenon where microorganisms develop the ability to resist the effects of drugs, including antibiotics, antifungals, and anti-parasitic medications. AMR is recognized as a complex issue, resulting in thousands of deaths per year worldwide [4]. The misuse of drugs has accelerated the emergence of AMR and increased the difficulty in treating diseases [5]. Hospitals, particularly intensive care units, are substantial breeding grounds for developing and spreading antibiotic-resistant germs. Antibiotic resistance enhances the morbidity and mortality rates associated with infections and significantly contributes to increased medical expenses due to extended hospital stays and the need for more expensive medications [6].

Antibiotic use and infection control procedures, along with interactions between patients, microorganisms, and the hospital environment, contribute to the development of resistance [7]. However, a question that arises is how this happens. Different types of bacterial resistance can be distinguished, including natural and acquired resistance, each with unique mechanisms. A significant challenge in medicine and public health is that resistance can develop through mechanisms such as genetic mutations and horizontal gene transfer [7]. When exposed to antibiotics, microorganisms can acquire resistance through natural selection. Susceptible bacteria are eliminated, allowing resistant strains to thrive and multiply. Resistance genes can be horizontally transferred between species of bacteria, accelerating the spread of resistance.

Additionally, specific pathogens may become resistant to multiple antimicrobial agents due to epidemic and endemic infections caused by these multiple-resistant strains, often followed by extensive antibiotic use in hospitals, particularly in intensive care units [8,9]. The World Health Organization classified critical pathogens in healthcare-associated infections into three groups based on global threat and urgency. The first and second groups, known as ESKAPE pathogens, encompass vancomycin-resistant Enterococcus faecium (VRE), methicillin-resistant and vancomycin-resistant S. aureus (MRSA/VRSA), carbapenem-resistant and third-generation cephalosporin-resistant Klebsiella pneumoniae, A. baumannii, P. aeruginosa, and Enterobacter spp. ESKAPE pathogens are hazardous due to their resistance to numerous antibiotics, including last-resort options like carbapenems and colistin [10-12]. Point prevalence surveys conducted in numerous countries offer a global perspective on AMR in hospitals, highlighting variations in resistance patterns [13]. The rapid global spread of multidrug-resistant bacteria, known as “superbugs,” has raised concerns about treatment options for infections that were once manageable [8,13]. A study on ten-year resistance trends in pathogens causing hospital infections also helps us understand how resistance has evolved over time, aiding in better infection control strategies [14]. In 2019, in the United States, the Centers for Disease Control and Prevention (CDC) regularly released reports on antibiotic resistance threats, providing valuable data on the situation in the country [15].

Identification of Resistance Patterns

Understanding the mechanisms by which the bacteria successfully defend themselves should ease the development of proper measures to optimize efficacy and increase the lifespan of antibiotics while decreasing antibiotic resistance [16]. We can mention the following among the mechanisms by which microorganisms defend against antibiotics. Multidrug efflux is one of the most significant systems that increase resistance to multiple antibiotics in bacteria. There are five major families of efflux pumps. First is the major facilitator superfamily, followed by the small multidrug resistance family (SMR), then the resistance-nodulation-cell-division family (RND), and the ATP-binding cassette family, and fifth, the multidrug and toxic compound extrusion family [17].

Tetracycline resistance is one of the most commonly used examples of efflux-mediated resistance, where Tet efflux pumps extrude tetracyclines using proton exchange as the energy source. More than 20 tet genes have been described, most of them harbored in MGEs (mobile genetic elements). Most of these pumps are preferentially found in gram-negative organisms with Tet (K) and Tet (L). Many of these pumps affect tetracycline and doxycycline [18]. Macrolide resistance is another significant phenotype of clinical relevance mediated by the efflux mechanism. The best-characterized efflux pumps are encoded by the mef genes (mefA and mefE) that extrude the macrolide class of antibiotics [19].

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Another important mechanism of resistance is to avoid the action of the antibiotic by interfering with their target site. Bacteria have evolved different tactics, including protection of the target (forbidding the antibiotic from reaching its binding site) and modifications of the target site, resulting in decreased affinity for the antibiotic molecule. Although some genetic determinants coding for proteins that mediate target protection have been found in the bacterial chromosome, most of the clinically relevant genes involved in this resistance mechanism are carried by MGEs. Examples of drugs affected by this mechanism include tetracycline (Tet[M] and Tet [O]), fluoroquinolones (Qnr), and fusidic acid (FusB and FusC) [20]. Furthermore, another mechanism is inactivation by a bacterial enzyme. Beta-lactamase production is a major resistance mechanism to beta-lactam antibiotics in clinical isolates. Such bacterial enzymes may cleave predominantly penicillins (penicillinases), cephalosporins (cephalosporinases), or both (beta-lactamases). Their production may be encoded within the bacterial chromosome, or the genes may be acquired on a plasmid or transposon (for instance, characteristic of an individual strain rather than the species).

Chromosomal beta-lactamases are the final mechanism of resistance. Although virtually all gram-negative bacilli possess a chromosomal beta-lactamase gene, certain species express insignificant amounts of this enzyme, and plasmid-mediated beta-lactamases and antibiotic permeability largely determine their susceptibility to beta-lactams. These include *E. coli*, Proteus mirabilis, Salmonella, Shigella, and H. influenzae. Klebsiella pneumoniae produces a chromosomal beta-lactamase, primarily a penicillinase; thus, these strains are frequently more susceptible to cephalosporins. The last group of species within the Enterobacteriaceae, including Enterobacter, indole-positive Proteus, Morganella, Serratia, and Citrobacter, produce an inducible chromosomal beta-lactamase, AmpC, that may be difficult to detect on initial susceptibility testing by that can mediate resistance to all currently available beta-lactams except for the carbapenems and perhaps cefepime [21,22].

Associated Risk Factors

AMR has emerged as one of the principal public health problems of the 21st century that threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses, and fungi no longer susceptible to the standard medicines used to treat them [23]. The hospital has historically been regarded as the epicenter of antimicrobial resistance. In many ways, it represents the ‘‘perfect storm’’ for the emergence and spread of antimicrobial resistance: acutely and chronically ill patients with indwelling devices are exposed to high levels of antibiotic use and busy hospital staff that contact multiple patients daily [24]. Some of the factors that contribute to the development of antimicrobial resistance are:

i. An increasing number of pathogenic organisms are resistant to one or more antimicrobial drugs.

ii. The overuse of antibiotics, inappropriate use, inadequate dosing, and poor adherence to treatment guidelines.

iii. Self-medication among the general population.

iv. Presence of highly susceptible immunosuppressed patients (e.g., Acquired Immune Deficiency Syndrome patients, cancer patients, or transplant recipients) and fragile elderly patients, invasive surgical procedures and intensity of clinical therapy, lengthy stay in hospital, failure to control infections spread from patient to patient [25].

v. Widespread and prolonged use of antimicrobials for therapy and or prophylaxis in hospitals

vi. Antimicrobial use in food-producing animals and aquaculture for growth promotion and disease treatment or prevention is probably a significant contributor to the overall resistance problem [23].

Some data favor methicillin-resistant Staphylococcus aureus infection, constituting risk factors such as differences in the availability and use of antimicrobials, incidence of HIV infection (a risk factor for MRSA colonization), and infection control practices, which could explain the variation between countries [26]. Risk factors also predispose to colonization and subsequent infection by MRSA, such as chronic skin lesions [26]. Likewise, people infected with the human immunodeficiency virus (HIV). They have a 6 to 18 times higher risk of MRSA infections than the general population [27]. In a prospective, matched case-control study, they found factors independently associated with post-discharge MRSA infection. These included MRSA colonization, discharge to a nursing home, a chronic wound post-discharge period, and discharge with a central venous catheter or different invasive devices in place [28]. On the other hand, in the scenario of gram-negative bacteria, the risk factors for acquiring ESBL and CPGNB include previous and recent use of antibiotics, residence in long-term intensive care centers, admission to intensive care, the presence of indwelling medical devices or wounds, poor functional status, advanced age, solid organs or stem cells transplant, and receive medical care in or travel to endemic areas [29,30].

Management and Prevention Strategies

A global pandemic of resistant S. aureus and Enterococcus species currently poses the most significant threat among gram-positive pathogens. Gram-negative pathogens are particularly worrisome because they are becoming resistant to nearly all the antibiotic drug options available, creating situations reminiscent of the pre-antibiotic era. The most severe gram-negative infections occur in healthcare settings and are most commonly

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caused by Enterobacteriaceae (mostly Klebsiella pneumoniae), Pseudomonas aeruginosa, and Acinetobacter. MDR gram-negative pathogens are also becoming increasingly prevalent in the community. These include extended-spectrum beta-lactamase-producing Escherichia coli and Neisseria gonorrhoeae [31,32].

Treatment of MRSA

compared the data from reviewing reports from 2017 to 2022 in a systematic review that summarized treatment options for MRSA, comparing their efficacy and cost-effectiveness [33]. Although they focused on vancomycin and daptomycin, which are the current Infectious Disease Society of America (IDSA)-recommended antibiotics for MRSA bacteremia treatment, a deep dive into the newer agents revealed better efficacy and treatment outcome in the combination of ceftaroline (β-lactam) with daptomycin compared to traditional standard monotherapy (vancomycin/daptomycin monotherapy).

Also, the IDSA recommended high-dose daptomycin (8-10 mg/kg) therapy for MRSA bacteremia treatment to be more effective in cases with vancomycin-reduced susceptibility. Moreover, they found no trial or study describing ceftaroline as a monotherapy to compare its efficacy in MRSA bacteremia with the current standard therapy. More large-scale clinical trials are needed to explore in-depth effectiveness and adverse effects to decide on newer agents like β-lactams to use as routine therapy for MRSA bacteremia [33].

Treatment of Pseudomona aeruginosa, Acinetobacter baumannii, Klebsiella pneumoniae: The 2022 review of "New antibiotics for Gram-negative pneumonia" by [32]. provided an overview of newly approved antibiotics for treating pneumonia caused by Gram-negative bacilli. Ceftazidime-avibactam, imipenem-sulbactam, and meropenem-vaborbactam have potent activity against some of the carbapenem-resistant Enterobacterales, especially Klebsiella pneumoniae carbapenemase producers. Several novel antibiotics have potent activity against multidrug-resistant Pseudomonas aeruginosa, such as ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relabactam and cefiderocol. Cefiderocol may also be essential in managing pneumonia caused by Acinetobacter baumannii, along with plazomicin and eravacycline [32].

Treatment of VRE

The two leading alternatives for vancomycin-resistant enterococci (VRE) and VRSA treatment are linezolid and daptomycin, with clinical success rates of 50-80% as a first-line drug and 50-59% as salvage therapy for VRE bacteremia, respectively [32]. The evidence suggests that daptomycin should be used as front-line therapy against vancomycin-resistant E. faecium, causing severe infections. Due to the lack of reliable measurement on MIC, daptomycin should be used in high doses (10–12 mg/kg), regardless of the MIC level within the susceptibility range (< 4 μg/ml). Nonetheless, in severe diseases affecting critically ill patients and those with severe compromise of the immune system (e.g., neutropenia), combination with β-lactams (i.e., ampicillin) should be considered as definitive therapy [30].

8.4. Preventive measures

Resolving the issues linked to AMR requires the implementation of suitable activities supported by a strong rationale for their cost-effectiveness as well as widespread benefits. Organizations, including intergovernmental, professional, non-governmental, industry, and academia, each have significant roles to play in enhancing and transforming such knowledge into practice. Understanding how AMR moves in the network of humans, animals, food, water, and the environment is relevant for developing new tools, guidelines, and laws to regulate AMR [34].

In 2015, an alliance of the WHO, the Food and Agriculture Organization of the United Nations, and the World Organization for Animal Health developed a Global Action Plan (GAP) to: "improve awareness and understanding of AMR through effective communication, education and training, strengthen the knowledge and evidence base through surveillance and research, reduce the incidence of infection through adequate sanitation, hygiene and infection prevention measures, optimize the use of antimicrobial medicines in human and animal health, and, develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines and other interventions [35].

Targeted hygiene

Targeted hygiene is a risk management system developed for home and everyday settings during the 1980s. Targeted hygiene means focusing on hygiene practices in places and at times ("risk moments"). The critical risk moments within home and everyday settings include food handling, using the toilet and changing a baby's diaper/nappy, touching surfaces frequently touched by others, coughing, sneezing and nose blowing, handling and laundering clothing and household linen, caring for domestic animals, disposing of refuse, and caring for an infected family member who is shedding infectious microbes into the environment. An important aspect of targeted hygiene is hygienic cleaning—as opposed to visible cleaning—to break the chain of infection. This is achieved using hygiene procedures (products plus process) to reduce pathogenic microorganisms on critical surfaces. Several methods exist to achieve such reduction in potential pathogens: mechanical/physical removal using dry wiping, soap, or detergent-based cleaning together with adequate rinsing, inactivation or eradication using a disinfectant on hard surfaces or an alcohol-based sanitizer on the hands, or a physical process such as heating (to ≥60°C/140°F) or ultraviolet treatment. Most frequently, a combination of these approaches is likely to be used [36].

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Antibiotic use in animals

Antibiotic resistance is caused by excessive and improper usage (inappropriate selections, insufficient dosing, and unclear obedience to medication guidance). However, human medication in the population and clinics, animal farming and agricultural sectors, and the environment are the four major sectors that influence the emergence of antibiotic resistance, according to research findings. Antimicrobial residues such as tetracycline, ciprofloxacin, enrofloxacin, and amoxicillin were identified in a significant percentage of poultry meat and eggs intended for human consumption [36]. Although antimicrobials are strictly sold on prescription in the developed world, antimicrobials are substantially cheaper and readily available over the counter (without prescriptions) in developing countries, thus conducting its use for growth promotion and infection prevention in animals. WHO recommends reducing and restricting medically essential antimicrobials in food animals for disease prevention and growth promotion. Echoing the WHO recommendations, the UN FAO action plan on AMR focuses on surveillance and monitoring, strengthening governance, and promoting good practices of optimal use of antimicrobials in food and agriculture [37].

Antibiotic duration

Guideline-concordant antibiotic selection is a vital stewardship target as it can improve "drug–bug" matches and reduce side effects. Shortening therapy to the minimum effective duration reduces antibiotic exposure and minimizes the risk of resistance and adverse events. Recent editorials have advocated for shorter courses of antibiotic therapy. Historically, 7, 10, or 14-day courses were the norm for many conditions. However, shorter durations of therapy are equally effective in several conditions, including community-acquired pneumonia, pyelonephritis, acute chronic obstructive pulmonary disease exacerbations, and sinusitis [38].

Communication skills training

Communication skills training for clinicians can improve antibiotic use. These trainings teach clinicians to effectively communicate with patients to understand patient concerns and expectations, provide information on expected disease course and recommended treatment options, and provide a contingency plan if symptoms do not improve [38].

Rapid and point-of-care diagnostic tests

When rapid diagnostic, including point-of-care, tests are available, have good sensitivity and specificity, and are not cost-prohibitive, they can help guide disease diagnosis and management, improving antibiotic prescribing. Testing should only be done if the clinical presentation is consistent with bacterial infection and test results will influence management [39].

Active monitoring and delayed prescribing

Active monitoring (also called watchful waiting) and delayed prescribing are treatment strategies that engage patients/caregivers to observe illness progression and return (active monitoring) or fill an antibiotic prescription (delayed prescribing) if symptoms do not improve or worsen [39].

Emerging Technologies and Future Directions

The most valuable approach is the rational design of new entities from novel chemical classes that influence new targets. Additionally, researchers are exploring various combinations of existing drugs with other molecules, such as efflux pump inhibitors. It is possible to create new and effective agents or compounds that can prevent invasiveness or reduce resistance by using the structures of natural products as a basis. Natural products have a wide range of structures, many of which have been shown to have anti-invasive properties or work well with traditional drugs. The application of nanotechnology also represents an excellent alternative for improving existing anti-invasive drugs because nanomaterials exert cytotoxicity through various mechanisms [40]. Small alterations to the target molecule, such as a point mutation in the ribosomal protein, can cause antibiotics to become ineffective. The multitude of antimicrobials and resistance mechanisms make testing for antimicrobial susceptibility complex. Genotypic methods that rely on nucleic acids can only identify resistances that are specifically searched for, and the identified resistance genes may not necessarily be from the pathogenic organism itself.

In principle, methods based on Nucleic Acid Amplification Technologist (NAAT), nucleic acid hybridization, or immunodiagnostics allow the use of non-purified polymicrobial clinical samples. Short cultivation with a pre-determined antibiotic load followed by NAAT (e.g., isothermal amplification) can reveal antimicrobial resistance and even provide a rough estimate of the minimal inhibitory concentration (MIC) for the tested antibiotics [41]. A promising approach for identifying and blocking infectious agents is using nucleic acid-based aptamers, which can specifically recognize these agents and inhibit their functions. To develop such aptamers, scientists use the systematic evolution of ligands by exponential enrichment (SELEX) technologies, which involve a process of iterative enrichment to identify aptamers that can detect specific pathogens [42]. Nanocarriers can also be used to selectively deliver high concentrations of antibiotics locally, thus avoiding systemic side effects. Success with these strategies has been limited, but it is expected that with more research and advancement of technology, nano delivery can become an important tool to overcome bacterial resistance [43].

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Conclusion

The global challenge of antimicrobial resistance (AMR) has reached a critical juncture, posing a significant threat to our ability to combat infectious diseases effectively. This review has highlighted the multifaceted nature of AMR, emphasizing its prevalence in hospitals and healthcare settings. We've delved into the intricate resistance mechanisms, ranging from efflux pumps to target site modifications and enzymatic inactivation, displaying the adaptability of microorganisms in the face of antibiotic pressure. AMR is not confined to one specific pathogen or setting but has become a global concern, with multidrug-resistant "superbugs" spreading rapidly and threatening the effectiveness of our last-resort antibiotics. Identifying resistance patterns and associated risk factors has shed light on the complex interplay of factors driving AMR, including overuse of antibiotics, immunosuppressed patients, and the role of various environmental factors.

Efforts to manage and prevent AMR encompasses a range of strategies, from optimizing antibiotic treatment regimens to implementing targeted hygiene practices and regulating antibiotic use in animals. Recent developments in the treatment of resistant pathogens, such as MRSA and multidrug-resistant Gram-negative bacteria, show promise, but continued research and clinical trials are essential to explore their full potential. The future of combating AMR lies in emerging technologies and innovative approaches, such as the rational design of new antibiotics, the use of nanotechnology, and the development of nucleic acid-based aptamers. Additionally, the importance of communication skills training for healthcare professionals and implementing rapid diagnostic tests must be considered to reduce unnecessary antibiotic use.

In this critical battle against AMR, collaboration between healthcare professionals, researchers, policymakers, and the public is paramount. The Global Action Plan and the united efforts of international organizations underscore the urgency of addressing this global health crisis. By embracing these strategies and fostering a renewed dedication to responsible antimicrobial use, we can strive for a future where effective treatment of infectious diseases remains within our reach. Our collective commitment to understanding, addressing, and mitigating antimicrobial resistance is more crucial than ever.

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