Challenges and solutions for the management of drug-resistant Nosocomial infections

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ABSTRACT

In hospitals, healthcare-associated infections (HAI), also referred as nosocomial infections (NI), pose a significant challenge, leading to prolonged hospitalization, increased healthcare costs, and mortality. Pathogens can be transmitted through high-touched surfaces, healthcare worker hands, and contaminated medical equipment. These infections are often caused by Multi-Drug Resistance Organisms (MDROs), which are bacteria resistant to multiple antimicrobial agents. Patients with higher illness severity scores, older age, and longer ICU stays are at increased risk. The most common side effect of healthcare is nosocomial infections, which can happen in any setting. Bacterial, fungal, and viral infections are potential causes for them, spread through direct or indirect contact. MRDOs, such as Methicillin-resistant Staphylococcus aureus (MRSA), Vancomycin-resistant Enterococci (VRE), and bacteria that produce Extended-spectrum beta-lactamases (ESBLs), pose a significant problem because of their antibiotic resistance. Preventive measures such as air filtration, hand hygiene, and environmental cleaning are important. Enhanced hand cleanliness, implementing contact precautions, and surveillance are crucial in managing MDROs. It is essential to use antibiotics judiciously and implement appropriate clinical measures. Further research is necessary to combat the proliferation of resistant strains. In conclusion, nosocomial infections caused by MDROs have significant public health implications. Effective prevention, control, and diagnosis are crucial in managing these infections. Preventive measures and proper antibiotic use are essential in controlling the spread of resistant bacteria.

Keywords: Nosocomial infection, Multi-drug Resistance, VRE, MRSA, ESBL

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Introduction

Healthcare-associated infections (HAI) generally refer to adverse occurrences stemming from healthcare facilities. Within the hospital environment, pathogenic microorganisms pose a significant challenge to proper operations (1).

Nosocomial infections (NIs) contribute significantly to mortality rates and can lead to extended hospital stays, as well as a considerable rise in healthcare expenses (2). Surfaces in hospitals that come into close contact with patients, like bed rails, bedside tables, handles, and tap handles, are considered easily contaminated and can transfer pathogens to patients. Additionally, items such as healthcare workers' cell phones, computers, protective lead garments, and oxygen humidifiers used in operating rooms may also play a role in transmitting pathogens. Healthcare workers' hands are critical in spreading infections from one patient to another through contact with contaminated surfaces or patients during caregiving activities (2). Regrettably, the use of broad-spectrum antibiotics is strongly linked to the existence of particular Multi-Drug Resistance (MDR) bacteria, both for initial and final treatment.

The development of nosocomial infections is associated with similar patient risk factors, such as higher illness severity scores, advanced age, respiratory insufficiency, and longer stays in the intensive care unit (ICU). Certain exposures in the ICU, like endotracheal intubation and central venous catheterization, also raise the risks of infection. Bacterial pathogens are the most frequently identified causative agents (3).

Microorganisms that are resistant to one or more classes of antimicrobial agents are known as Multi-Drug Resistance Organisms (MDROs). While some MDROs, like MRSA and VRE, are named after a single aspect, they typically exhibit resistance to most antimicrobial drugs. Healthcare facilities need to pay particular attention to these highly resistant organisms (4).

Nosocomial infections

Patients under medical care experience nosocomial or healthcare-associated infections, which are the most prevalent adverse outcome in healthcare impacting patient safety. They impose significant morbidity, mortality, and financial burdens on patients, families, and healthcare systems. Multidrug-resistant organisms are another complexity observed in association with healthcare-associated infections (HAIs) (5). Hospital-acquired infections (HAIs) are infections that appear in an inpatient or outpatient setting within 48 hours of hospital admission, within 30 days of receiving medical care, or up to 90 days after certain surgical procedures (6-8). Hospital infections are mainly the result of contaminated medical equipment during surgery or from antibiotic-resistant germs, affecting patients, professionals, and hospital staff (9). There are various factors that contribute to hospital infections, with the most significant being: being under the age of 1 or over the age of 65, experiencing malnutrition, being admitted to the intensive care unit as an emergency, staying in the hospital for over 7 days, using a urinary catheter, venous catheter, arterial catheter, suction, tracheal tube, undergoing surgery, taking immunosuppressive drugs, and being in a coma (10). The most common organ involved in hospital infections is the urinary system, followed by the respiratory and circulatory systems (11, 12).

The Centers for Disease Control (CDC) collaborates with the National Health Care Safety Network to categorize nosocomial infection sites into 13 types, encompassing 50 specific locations. As per the National Health Care Safety Network in collaboration with the Centers for Disease Control, hospital-acquired infections are generally categorized into 13 different types based on the infection site, which is identified through clinical and biological criteria. These types include surgical site infections, respiratory tract infections, bloodstream infections, hospital-acquired fungal infections, urinary tract infections, central nervous system infections, hospital-acquired pneumonia (both bacterial and viral), Mycobacterium tuberculosis, various types of lung infections including legionnaires, and aspergillosis. Below are some of the other common types of infections (13).

The occurrence of infections in healthcare settings is due to a variety of microorganisms, each with the ability to cause infection. Bacterial infections account for around ninety percent of all infections, with protozoa, fungi, viruses, and mycobacteria playing a lesser role in causing infections. (14). The most common infections found in hospitals are caused by Streptococcus, Acinetobacter, Enterococcus, Pseudomonas aeruginosa (P. aeruginosa), Coagulase-negative Staphylococcus, Staphylococcus aureus (S. aureus), mostly Bacillus cereus, Legionella, and members of the Enterobacteriaceae family including Proteus mirabilis, Klebsiella pneumonia (K. pneumonia), Escherichia coli (E. coli), and Serratia marcescens. Enterococci, P. aeruginosa, S. aureus, and E. coli are the key players in these infections (15). HAIs can be transmitted through direct and indirect means. Direct contact includes touching an infected person, animal, or source of infection. The main mode of disease transmission is through contaminated hands. Indirect transmission occurs without direct contact between an infected and healthy person, as

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transmissible agents can spread the disease. Pathogens on surfaces and objects can also transmit infectious agents. Additionally, pathogens from coughs and sneezes of patients can be carried in aerosols and transmit diseases (16).

Challenges of resistance in hospital strains

"Nosocomial infections" is one of the most concerning topics nowadays. These types of infections have a high mortality rate (17). In the United States, nosocomial infections rank as the sixth leading cause of death. Furthermore, a significant number of patients died from nosocomial infections in 2002, highlighting the severity of these aggressive infections. One of the most noteworthy factors leading to the increased mortality of NIs is the resistance building up in different microorganisms, leading to the appearance of multidrug-resistant organisms (MDROs). These mentioned organisms dull the effect of a vast range of antibiotics, thus challenging to treat (18). Some of the most crucial MDROs include Staphylococcus aureus, Coagulase-negative Staphylococci, and Aerobic Gram-negative bacilli. Due to their resistance, these organisms can result in recurrent infections like urinary tract infections, infected ulcers, and ear infections. Therefore, it is essential to implement infection control measures in healthcare settings to prevent their spread, covering various aspects of hospitals or healthcare facilities. But one of the most important measures is the development of the awareness and knowledge of the personnel against emerging infectious diseases and how to protect the patient and themselves against the mentioned diseases. Not only should the staff be properly educated, but there must be regulations and standards on protection against model respiratory, gastrointestinal, body fluid, and insect-borne diseases (19).

Although patients are at risk of nosocomial infections, adults, children, and immune-compromised patients are among the most vulnerable ones. There are several preventive measures taken. One simple thing is air filtration and purification in healthcare facilities (6). Because aerosols are one of the most prevalent ways of infection spread (20).

MRSA

One of the most concerning strains of drug-resistant S. aureus is Methicillin-resistant Staphylococcus (MRSA). This specific strain has led to increased mortality and increased hospital stays, subsequently causing financial and clinical problems for both the staff and the patients and their families (21). As for the bacteria S. aureus, most of the antibiotic-resistant strains were found in UTI (22). It's also noteworthy that recent MRSA strains are changing in a way so they're not only hospital-acquired but they're also acquired through day-to-day interactions of people (23). If MRSA is involved, the bacteremia caused by such strain can render the treatment procedure challenging (24). Nosocomial infection rates have been fluctuating ever since and this phenomenon may be for several reasons; such as the reduction of prevalence or the improvement of the healthcare system. But it's essential to know that nosocomial infections are not caused only by bacteria. There are fungi included as well. But between all the microorganisms, the leading causes of nosocomial infection of the respiratory tract are gram-negative Acinetobacter, Pseudomonas aeruginosa, Staphylococcus aureus, and fungi (25).

VRE

Another important nosocomial infection causes are Vancomycin-resistant Enterococci. These strains can be colonized through contact with healthcare professionals (HCPs) (26). prior antimicrobial use, exposure to other patients, and contaminated surfaces with VRE (27). Considering all the different colonization ways, VRE can lead to longer hospital stays, thus becoming a financial hindrance for not only the patients but also the personnel. Not only this, the excess mortality reported by VRE (28) is alarming. Enterococci have been among the most reported pathogens so many of the advanced countries. ICUs are among the most common places of VRE colonization (29). More importantly, the colonization of VRE is not always pathogenic and symptomatic. These strains can get colonized in the GI tract asymptomatically. Thus, leading to the further spreading of the infection mechanically (27).

ESBL

Extended-spectrum beta-lactamases (ESBLs)-producing strains are one of the most serious causes of nosocomial infections. Due to the increased resistance against the Beta-Lactamase antibiotics, they have higher pathogenicity (30). Therefore, these strains have higher rates of mortality and morbidity. In a way almost 10% of all nosocomial infections are caused by these certain strains, causing UTI, sepsis, pneumonia, etc (31, 32). The infection of ESBL is so severe that most of the patients in the last 2 decades have been admitted to ICU.

Prevalence of Methicillin-resistant Staphylococcus aureus (MRSA)

Staphylococcus aureus, a highly aggressive pathogen, causes numerous human infections globally. This bacterium is gram-positive, facultatively anaerobic, and lacks spores. It is commonly present in the skin, particularly in damaged skin, soft tissue, bones, joints, the navel of newborns, and the respiratory tract (33, 34). Metastatic infections like infective endocarditis (IE), septic arthritis, and osteomyelitis are frequently caused by S. aureus bacteremia. Moreover, it can result in complications such as sepsis and septic shock

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(34). Ogston first discovered Staphylococcus aureus in exudate from a foot abscess in the 1880s, and Rosenbach later officially characterized it (35).

Beecham introduced methicillin in 1959. However, just about a year later, methicillin-resistant Staphylococcus aureus was discovered in England. Since the 1990s, it has quickly proliferated in the community (33, 35). The production of beta-lactamase enzyme does not affect methicillin resistance. The mecA chromosomal gene is responsible for the antibiotic resistance in this strain, as it codes for the penicillin-binding protein PBP2a, which has low affinity for semi-synthetic penicillins. These factors contributing to methicillin resistance are carried by a movable genetic element known as the SCCmec cassette chromosome (SCCmec), which is inserted into the chromosome of S. aureus (36).

MRSA is considered one of the most serious multidrug-resistant threats and is prevalent as a hospital-acquired infectious disease, causing anything from superficial wound infections and food poisoning to pneumonia, infective endocarditis, bacteremia, and more. It is a systemic infection and effectively adjusts to the human host and healthcare setting (35, 37, 38). The occurrence of nosocomial infections is a worldwide issue, and various factors play a role in their development. MRSA can spread readily through direct or indirect contact with patients or healthcare staff (37).

Research indicates that MRSA accounts for between 13 and 74% of Staphylococcus aureus infections worldwide, with an estimated frequency of 43% in Iran. Specifically, the World Health Organization (WHO) is actively working on implementing a global action plan to address antimicrobial resistance by establishing strategic objectives centered on raising awareness, conducting surveillance, and researching antimicrobial resistance. Furthermore, the initiative seeks to encourage the advancement of new medications, diagnostic tools, and vaccines (36, 39).

Prevalence of vancomycin-resistant Enterococci (VRE)

Vancomycin, now known as a compound, was isolated from soil found in the interior forest of Borneo more than fifty years ago (40). That is one of the oldest antibiotics in clinical use for nearly 60 years (41). Vancomycin is a complex three-ring glycopeptide antibiotic with a molecular weight of approximately 1500, which is used by injection, oral, and eye drops, and is active against staphylococci, streptococci, and other gram-positive bacteria (42). By targeting the building blocks of bacteria, it blocks cell wall formation (43).

Gram-positive enterococci are cocci that can survive with or without oxygen and are part of the normal bacterial population in the gastrointestinal tract. Enterococci develop resistance to different antimicrobial agents through both inherent and acquired methods (44-46).

Antimicrobial resistance is currently a significant global public health issue. Vancomycin-resistant Enterococcus (VRE) was identified in the mid-1980s, over 30 years after vancomycin was first used clinically. Defines healthcare as "an infection that occurs in a patient during care in a hospital or other healthcare facility that was not present or incubating at the time of admission. Prolonged, primarily in patients with severe underlying disease." The duration of hospitalization, weakened immune system, younger age, administration of ceftriaxone and vancomycin, and prior use of antibiotics have been demonstrated to confer a specific advantage to certain microorganisms in the intestinal flora either through genetic mutation or the uptake of external genetic material. Enterococci develop resistance to vancomycin by acquiring genes from plasmids or transposons, allowing the bacteria to circumvent the formation of antibiotic-sensitive cell walls, and are commonly responsible for infections acquired in hospital settings (44-48).

Between 1989 and 1993, there was a rise in the proportion of nosocomial Enterococcal infections attributed to VRE reported to the National Nosocomial Infection Surveillance System by the Centers for Disease Control and Prevention, increasing from 0.3 to 7.9% (6).

Factors that increase the risk of bacteremia consist of malignancy, evaluation of chronic health conditions, low levels of neutrophils, extended hospitalization, use of antibiotics, and prior treatment with drugs that can combat anaerobic organisms. The average duration of antibiotic treatment is linked with VRE infections (6).

The presence of VRE infection is linked to a rise in mortality, as demonstrated by a 2.5-fold increase in mortality (11).

Prevalence of ESBLs

ESBL-producing bacteria play a crucial role in causing nosocomial infections, particularly in the ICU of healthcare facilities (49). Prolonged and consistent exposure of gram-negative bacteria from the Enterobacteriaceae family (particularly Klebsiella pneumoniae and Escherichia coli) to beta-lactam antibiotics results in genetic mutations in the TEM and SHV enzyme-encoding genes (which are the most prevalent among various types of ESBLs), ultimately leading to the development of a category of beta-lactamases known as extended-spectrum beta-lactamases (ESBLs) (49-52). It has been shown that in addition to new mutations, gene transfer through plasmid or inheritance can also lead to the appearance of ESBL-producing bacteria (53). ESBLs typically cause the breakdown and deactivation of a broad spectrum of beta-lactam-based antibiotics by cleaving the beta-lactam ring. This includes third-generation

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cephalosporins such as ceftriaxone and cefixime, as well as penicillins and Aztreonam (51, 52). Members of the Enterobacteriaceae family that produce extended-spectrum beta-lactamases are recognized as among the most significant multidrug-resistant (MDR) organisms in hospital settings. They contribute to economic and social challenges, including increased treatment expenses and a higher mortality rate. Also by creating limitations in the treatment of bacterial diseases, it has created the need for new drugs and antibiotics (12, 53). In Sudan, research found that the main ESBL production occurred in Escherichia coli and Klebsiella pneumonia, with reported percentages of 38% and 34% respectively (54). The occurrence of ESBL-producing bacteria within the Enterobacteriaceae family was found to range from 21.6% to 29.3% in a research study conducted in Persian Gulf countries (53). In a study in Bangladesh, the prevalence of ESBL-producing Klebsiella is reported as 45% (55). In Japan, the rate of ESBL-producing Enterobacteriaceae infection among patients who acquired the infection from the hospital was reported as 60.4% (56). In Iran, studies conducted in Shahroud, Isfahan, Shahrekord, and Tehran reported that the percentage of isolates producing extended-spectrum beta-lactamases was 50%, 60.4%, 64%, and 55.4% respectively (49, 51, 57, 58). Also, in Mazandaran, out of 149 isolated bacterial isolates, 35 were ESBL producers (59). In another study, with the participation of hospitals in different cities of Iran (Tabriz, Isfahan, Shiraz, Sari, Mashhad, Sandaj, and Ahvaz), 61% of isolates of K. pneumonia and 35% of E. coli were produced ESBL (60). Due to the high prevalence of antibiotic resistance, especially among members of the Enteroacteraceae family, which cause nosocomial infections, taking extensive measures regarding infection control should be considered (59).

Strategies to prevent the development of resistance in the hospital

Surveillance can reduce infection rates by providing infection trends, early warning of outbreaks, "Assessment" and checking feedback to health care work, and finding protective factors or risks for Nis (61).

A variety of methods and recommendations are available to stop the transmission of MDR pathogens, including common practices like hand hygiene and precautions for patients with MDR organisms. Additional measures that could lower the occurrence of these organisms consist of antimicrobial surveillance programs, cleaning the environment, and procedures for decolonization (62).

MDROs are commonly spread from one person to another via the hands of healthcare staff, as supported by extensive epidemiological data.

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In healthcare settings, reducing infections lessens the impact of MDROs. To prevent antibiotic resistance, it is crucial to implement appropriate clinical measures as part of routine patient care.

These measures encompass the effective management of vascular and urinary catheters, the prevention of lower respiratory tract infections in intubated patients, accurate identification of infectious causes, and careful selection and usage of antibiotics. Successful management of MDROs involves enhancing hand hygiene, employing contact precautions until patients test negative for a specific MDRO, conducting active surveillance (ASC), providing education, enhancing environmental cleaning, and improving communication about patients with MDROs within and between healthcare facilities (63, 64). The increasing virulence of these strains has a direct relation with the increased mortality (65). ESBL-producing bacteria, most importantly gram-negative ones, hydrolyze β lactam ring, rendering β lactam antibiotics ineffective (66). Subsequently, they are resistant to most of the third-generation cephalosporins (67, 68).

ESBL production among bacteria like K. pneumoniae is not focused on one country. These strains are prevalent in different continents such as Europe, the Western Pacific, the United States, and Latin America. The resistance of ESBL-producing strains is not limited to only one specific type of antibiotic. The countries that have had the highest Carbapenem resistance, have also had the highest resistance for other antimicrobial groups (69).

Conclusion

In today's world, the misuse of antibiotics has led to the emergence of multi-resistant bacterial infections in healthcare settings, making nosocomial infections and drug resistance a significant global health concern (46, 70). Among the pathogens that cause nosocomial infections, MRSA, VRE, and ESBL are considered some common and important risk factors for patients and health workers (33, 49, 71). The impact of these infections includes higher mortality rates, longer hospital stays, and increased treatment expenses.

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Additionally, the overuse of antibiotics to address microbial pathogens is restricted, leading to a demand for new medications (53, 70-72). Therefore, it is important to use effective methods of prevention, control, and diagnosis of resistant strains (73). To control this category of infections, in addition to the patients and the treatment staff, the hospital environment and the patient's specific equipment must be monitored. Also, performing periodic screenings and managing the appropriate use of antibiotics can be effective in controlling these infections. In addition, the use of gowns, gloves, masks, and Antiseptics in hospitals can be effective in preventing the transmission of these pathogens (71, 72). According to the results of this study, it can be seen that due to excessive use of antimicrobial agents around the world, new strains of resistant bacteria are spreading. So, extensive and specialized studies should be done in this field. Also, appropriate methods of prevention, control, and treatment should be considered in communities.

Ethical Issue

There was no ethical issue in this review.

Conflict of Interests

There was no conflict of interest in this study.

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