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Review Article

A review on Meropenem resistance: Current trends and clinical implications

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ABSTRACT

Antibiotic resistance has become a global healthcare crisis, posing a significant challenge to the effective treatment of bacterial infections. Meropenem, a broad-spectrum carbapenem antibiotic, has long been considered a last-line defense against multidrug-resistant pathogens. However, the emergence and spread of meropenem resistance represent a critical threat to public health, necessitating a comprehensive understanding of its current trends and clinical implications. This review provides a detailed analysis of the current state of meropenem resistance, Trends in Meropenem Resistance, Global prevalence and distribution of meropenem-resistant bacteria, Factors contributing to the spread and persistence of meropenem resistance, Impact of meropenem resistance on healthcare settings and patient outcomes encompassing both Gram-positive and Gram-negative bacterial strains. Clinical implications of meropenem resistance are far-reaching. Patients infected with meropenem-resistant strains often experience delayed and inadequate treatment, resulting in higher mortality rates and prolonged hospital stays. Efforts to combat meropenem resistance include antibiotic stewardship programs, infection control measures, and the development of novel antimicrobial agents. In conclusion, meropenem resistance is a critical issue that demands urgent attention from healthcare professionals, researchers, and policymakers. Understanding the current trends and clinical implications is paramount for implementing effective strategies to mitigate the spread of resistance, preserve the utility of meropenem, and ensure better outcomes for patients with severe bacterial infections. A comprehensive, multidisciplinary approach is essential to address this growing threat and safeguard the future of antibiotic therapy.

INTRODUCTION

Antimicrobial resistance (AMR) has emerged as a global public health crisis, compromising the effectiveness of many life-saving antibiotics. The overuse and misuse of antimicrobial agents have contributed to the development and spread of resistance among bacterial pathogens. AMR poses a significant challenge to healthcare systems

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worldwide, leading to increased morbidity, mortality, and healthcare costs.

Meropenem, a broad-spectrum carbapenem antibiotic, is commonly used in the treatment of severe infections caused by multidrug-resistant Gram-negative bacteria. However, the emergence and spread of meropenem-resistant strains have significantly limited its effectiveness. Meropenem resistance poses a critical threat to clinical practice as it compromises treatment options for serious infections, including those acquired in healthcare settings such as hospitals and intensive care units. Infections caused by meropenem-resistant bacteria are associated with higher rates of treatment failure, prolonged hospital stays, increased healthcare costs, and elevated mortality rates.

The objective of this review article is to provide a comprehensive overview of meropenem resistance, including its trends, and implications for clinical practice. The article aims to synthesize the current literature on meropenem resistance, highlighting global trends and the clinical implications for patient management. Moreover, the review will discuss diagnostic strategies for detecting meropenem resistance, strategies to combat resistance, and future research directions. By addressing these aspects, this review article intends to contribute to the understanding of meropenem resistance and provide valuable insights for clinicians, researchers, and policymakers.

2.TRENDS IN MEROPENEM RESISTANCE:

Meropenem resistance has been on the rise globally, posing a significant challenge in healthcare settings. There is a concerning trend of increasing rates of meropenem-resistant bacteria, including Enterobacteriaceae, Pseudomonas aeruginosa, and Acinetobacter baumannii. This rise in resistance can be attributed to factors such as widespread antibiotic use, inadequate infection control measures, and the international spread of resistant strains. Addressing this trend requires a comprehensive approach that includes antibiotic stewardship, improved surveillance, and the development of new treatment strategies to combat meropenem-resistant infections.

2.1. Global prevalence and distribution of meropenem-resistant bacteria:

The global prevalence and distribution of meropenem-resistant bacteria vary across different regions and healthcare settings. High-dose continuous infusion meropenem-based combination regimens could still be a valuable option for treating carbapenem-resistant Enterobacteriaceae (CRE) infections in specific circumstances [1]. Elderly people in long-term care facilities (LTCF) are at an increased risk of acquiring infections by multidrug-resistant organisms (MDROs), including carbapenem-resistant Enterobacterales (CRE) [2]. In a tertiary care hospital in China, the prevalence of carbapenem-resistant Enterobacteriaceae (CRE) was found to be high, particularly in various intensive care units (ICU) and surgical departments [3]. In US hospitals, the prevalence of carbapenem resistance (CR) among the most common Gram-negative bloodstream infection (BSI) pathogens was 3.5%, with variations based on organism, hospital ward, and geography [4]. The global prevalence and distribution of meropenem-resistant bacteria have escalated in recent years, presenting a substantial challenge to healthcare systems worldwide. The rise of resistant strains in both healthcare and community settings underscores the urgent need for comprehensive strategies to combat meropenem resistance. This requires robust surveillance, antimicrobial stewardship, infection control measures, and international collaboration to mitigate the spread of meropenem-resistant bacteria and preserve the efficacy of this vital antibiotic.

2.2 Factors contributing to the spread and persistence of meropenem resistance:

Multiple interconnected factors contribute to the spread and persistence of meropenem resistance. Addressing this issue requires a comprehensive approach that encompasses appropriate antibiotic use, rigorous infection prevention and control measures, enhanced surveillance and monitoring, and a deeper understanding of the environmental factors influencing resistance. Factors contributing to the spread and persistence of meropenem resistance include the ability of pathogens to acquire resistance genes and undergo genetic modifications. Bacteria can acquire resistance genes through horizontal gene transfer mechanisms such as conjugation, transformation, and transduction. This allows resistant traits, including meropenem resistance genes, to be rapidly disseminated among different bacterial species. [5]. The inappropriate use of meropenem and other broad-spectrum antibiotics can lead to the selection and proliferation of resistant bacteria. Overprescription, inadequate dosing, and failure to complete prescribed courses of treatment can all contribute to the development of resistance. According to a study conducted in West Africa, the overuse and abuse of antibiotics, as well as complex interactions between human health, animal husbandry, and veterinary medicine, have also played a role in the propagation and spread of resistant organisms [6].

Inadequate implementation of infection control practices, such as hand hygiene, proper disinfection, and isolation protocols, can facilitate the spread of meropenem-resistant bacteria within healthcare facilities.Moreover,inadequate healthcare infrastructure, such as insufficiently trained prescribers and inadequate diagnostic tools, has further exacerbated the problem in less developed countries [7]. Additionally, the uncontrolled drug sector, with antibiotics being sold over-the-counter, improperly stored, counterfeit, and/or expired, has contributed to the emergence of antibiotic resistance [8]. These factors highlight the need for effective health policies and interventions that target policy makers, prescribers, and users [9]. By addressing these factors, healthcare systems and policymakers can work towards mitigating the spread of meropenem resistance and preserving the effectiveness of this critical antibiotic.

2.3 Impact of meropenem resistance on healthcare settings and patient outcomes:

The review article also address the impact of meropenem resistance on healthcare settings and patient outcomes. Meropenem resistance has a significant impact on patient outcomes and healthcare settings. Patients with meropenem-resistant infections have a higher risk of death compared to those with no or drug-susceptible infections. Meropenem resistance has a significant impact on healthcare settings and patient outcomes.Factors such as prolonged hospital stays, invasive procedures, and the use of medical devices create opportunities for the transmission and persistence of resistant strains. Patients with meropenem-resistant Pseudomonas aeruginosa infections have a higher risk of in-hospital mortality compared to those with meropenem-susceptible infections [10]. When bacteria become resistant to meropenem, it reduces the available treatment options for infections caused by these pathogens. This can lead to prolonged illness, increased morbidity, and higher mortality rates among affected patients. They also experience longer hospital stays, increased for intensive care unit (ICU) admission, and higher total hospital costs [11]. Infections caused by meropenem-resistant bacteria are associated with higher rates of treatment failures and complications. Delayed or inadequate therapy can result in persistent infections, sepsis, organ damage, and other life-threatening complications. [12]. However, prior use of other antibiotic use was not found to be associated with the acquisition of meropenem-resistant infections [13]. In order to minimize the negative impact of antimicrobial therapy, strategies such as using optimal diagnostic procedures, streamlining or discontinuing therapy based on culture results, and using the shortest duration of therapy needed for documented infections should be implemented [14]. In addition, surveillance cultures and contact precautions or cohort nursing for patients colonized or infected by resistant strains are necessary to control the spread of antimicrobial resistance in healthcare settings .The appropriateness of antimicrobial therapy, considering the pathogen, site of infection, and pharmacokinetic properties, is essential in measuring the impact of resistance on patient outcomes .

3. CLINICAL IMPLICATIONS OF MEROPENEM RESISTANCE

Optimizing antimicrobial use, including using optimal dosing and minimizing unnecessary antibiotic use, is essential to minimize the negative impact of antimicrobial resistance . Infection control programs and competent microbiology laboratories are also vital in combating antimicrobial resistance and improving patient safety .

3.1 Therapeutic options and Efficacy of Meropenem against meropenem-resistant strains

Meropenem has shown efficacy against meropenem-resistant strains. In one study, the combination of meropenem with another carbapenem, doripenem, was found to be effective against carbapenem-resistant K. pneumoniae strains producing serine carbapenemases such as KPC and OXA-48 [15]. Another study developed a series of metallo-beta-lactamase inhibitors (MBLIs) that restored the activity of meropenem against NDM/IMP/VIM-producing Enterobacterales, including carbapenem-resistant strains [16]. Additionally, a study demonstrated that optimized two-step-administration therapy (OTAT) with meropenem, even in monotherapy, was effective against highly resistant bacterial isolates with meropenem minimum inhibitory concentrations (MICs) $\geq$ 16 mg/L [17]. Furthermore, a study found synergistic effects between meropenem and curcumin, a natural ingredient, against carbapenemase-producing strains of Klebsiella pneumoniae [18]. These findings suggest that meropenem can be effective against meropenem-resistant strains when used in combination with other antibiotics or inhibitors.

3.2 Impact on patient outcomes and mortality rates

Meropenem resistance has been shown to have a significant and negative impact on patient clinical outcomes, hospital admissions, and mortality rates. Studies have shown that patients infected with meropenem-resistant bacteria are at a higher risk of mortality compared to those with susceptible infections. The limited treatment options and delayed response to therapy contribute to this increased risk.Patients with carbapenem-resistant Acinetobacter baumannii (CRAB) pneumonia treated with meropenem-colistin combination therapy had higher in-hospital mortality rates compared to those treated with meropenem-tigecycline [19]. In patients with gram-negative infections, including carbapenem-resistant Enterobacterales (CRE), delayed initiation of meropenem-vaborbactam (MEV) therapy was associated with negative clinical outcomes (NCOs) and increased mortality [20]. Implementation of a meropenem antibiotic stewardship program (ASP) led to improved meropenem prescription adequacy, decreased meropenem consumption, and reduced rates of hospital-acquired multidrug-resistant bloodstream infections (BSIs) and 30-day all-cause mortality in MDR BSIs [21]. Patients infected with meropenem-resistant bacteria often require longer hospital stays. Extended hospitalization can increase the risk of healthcare-associated complications and infections.In patients with

Pseudomonas aeruginosa infections, meropenem resistance was associated with higher in-hospital mortality rates, longer hospital stays, increased ICU admissions, and higher total hospital costs [22]. Overall, meropenem resistance has a detrimental impact on patient outcomes and healthcare resources.

3.3Economic burden and healthcare costs associated with meropenem resistance

Meropenem resistance is associated with a significant increase in hospital costs and in-hospital mortality .Meropenem resistance in bacteria is not only a significant clinical concern but also imposes a substantial economic burden and increased healthcare costs. Patients with meropenem-resistant isolates had a higher risk of in-hospital mortality compared to those with meropenem-susceptible isolates [11]. Meropenem-resistant infections are associated with longer hospital stays due to the challenges in treating them effectively. Extended hospitalization results in increased costs related to room and board, nursing care, and other hospital services.The increase in mortality was accompanied by a longer length of stay and a higher percentage of patients requiring intensive care unit (ICU) admission. Patients with meropenem-resistant Pseudomonas aeruginosa experienced a 4-day increase in median length of stay and a higher percentage of ICU admissions. This is turn led to an overall increase in hospital expenditures . [23]. Among patients who were not admitted to the ICU, meropenem resistance was also associated with a significant increase in total hospital cost [24]. The economic burden of carbapenem-resistant Enterobacteriaceae (CRE) infections, including meropenem resistance, is substantial.The cost of CRE increases proportionally with the incidence rate, resulting in billions of dollars in costs for hospitals, third-party payers, and society .[25] meropenem resistance drives up healthcare costs through various channels, including more expensive treatments, prolonged hospitalization, additional medical interventions, and infection control measures. Addressing antimicrobial resistance, including meropenem resistance, is not only a medical but also an economic imperative to reduce the overall burden on healthcare systems and society.

4 STRATEGIES TO COMBAT MEROPENEM RESISTANCE

Strategies to combat meropenem resistance involve a multifaceted approach that includes antibiotic stewardship, surveillance, infection control, combination therapy, development of new antibiotics, alternative treatment options, and prevention of transmission.

4.1 Antibiotic stewardship programs and rational use of antibiotics

Antibiotic stewardship programs , particularly meropenem stewardship programs aim to optimize meropenem usage, such as dose optimization, combination therapy, and therapeutic drug monitoring.Studies have shown implementation of AMS to improve the rational use of meropenem. A study conducted in tertiary pediatric hospital have demonstrated that meropenem can be used as monotherapy for complicated, multi-drug resistant, gram negative bacterial infections due to its susceptibility profile, convenient dosing schedule, and minimum adverse effects [26]. A study conducted on tractable targets of Antimicrobial stewardship of meropenem have identified several targets for stewardship interventions, including supporting rationalization to carbapenem-sparing antimicrobials, restricting first-line meropenem usage, and selectively reporting meropenem susceptibility [27]. Implementation of a meropenem antibiotic stewardship program has been associated with improved prescription adequacy, decreased meropenem consumption, and reduced rates of hospital-acquired multidrug-resistant bloodstream infections and mortality [21]. Additionally, the use of an antimicrobial stewardship program has been found to be more effective in improving the prescription and efficacy of meropenem compared to conventional methods [28]. Overall, antibiotic stewardship programs play a crucial role in promoting the rational use of meropenem and optimizing clinical outcomes. By employing strategies in a coordinated manner, it is possible to mitigate the impact of meropenem resistance and preserve the effectiveness of this important antibiotic.

4.2 Development of novel antimicrobial agents and therapeutic approaches

The development of novel antimicrobial agents and therapeutic approaches to combat meropenem resistance is a critical global challenge. Several strategies have been proposed to address this issue. Immunotherapy, drug combination therapy, bacteriophage therapy, and CRISPR/Cas genome editing technology are some of the promising approaches discussed in the literature [29]. Non-antibiotic antimicrobial agents are also being explored as alternative therapeutic options [30]. Collaboration among stakeholders and the development of new antibacterial drug identification methods and strategies are crucial in fighting against antibiotic resistance [31]. Additionally, the approval of meropenem-vaborbactam, a carbapenem antibiotic with a novel beta-lactamase inhibitor, has shown promising results in treating carbapenem-resistant Enterobacteriaceae (CRE) infections [32]. Computational approaches for surveillance of antibiotic resistomes and the formulation of combinatorial drugs are also being explored [33]. Overall, a multidimensional approach involving novel therapeutic agents, alternative options, and surveillance methods is necessary to combat meropenem resistance effectively.

4.2.1 New β-lactamase inhibitors and combination therapies

β-lactamase inhibitors are compounds that are used in combination with β-lactam antibiotics to enhance their effectiveness against β-lactamase-producing bacteria. β-lactamases are enzymes produced by some bacteria that can inactivate β-lactam antibiotics, such as meropenem. By inhibiting these enzymes, β-lactamase inhibitors restore the activity of β-lactam antibiotics and improve their efficacy against resistant bacteria.

New β-lactamase inhibitors and combination therapies have been investigated for their effectiveness against meropenem resistance in Gram-negative bacteria. One study evaluated a novel β-lactam-derived β-lactamase inhibitor, BP2, co-administered with meropenem, and found that it potentiated the synergistic activity of meropenem against virulent Enterobacterale strains expressing serine and metallo-β-lactamases (MBL) genes [34]. Another study focused on Xeruborbactam, a cyclic boronic acid β-lactamase inhibitor, and its activity against Enterobacterales and A. baumannii when combined with meropenem. The study found that the activity of Xeruborbactam was best described by the % 24h free Xeruborbactam plasma concentrations exceeded 1 mg/L and 24h free Xeruborbactam plasma AUC [35]. Additionally, fisetin, a natural compound, was found to inhibit the activity of NDM-1, a metallo-β-lactamase, and when combined with meropenem, it attenuated meropenem resistance in NDM-1-positive Escherichia coli [36]. These studies highlight the potential of β-lactamase inhibitors and combination therapies in overcoming meropenem resistance in Gram-negative bacteria.

4.3 Infection prevention and control measures

Infection prevention and control measures play a crucial role in addressing the rise of meropenem resistance in Enterobacteriaceae. Emphasizing effective infection prevention and control measures is crucial in combating meropenem resistance. This includes promoting strict adherence to hand hygiene practices, implementing appropriate isolation precautions, and ensuring proper disinfection and sterilization protocols. By reducing the transmission of resistant bacteria, these measures can help contain the spread of meropenem resistance within healthcare facilities and the community.Screening of at-risk patients, especially in critical care areas, using appropriate laboratory methods is recommended before administering antibiotics [37].

Hand hygiene is considered one of the most effective measures to prevent the spread of infections in healthcare settings. It helps reduce the transmission of bacteria between patients, healthcare workers, and the environment, thereby preventing hospital-acquired infections. By practicing proper hand hygiene, healthcare workers can minimize the spread of antibiotic-resistant bacteria, including those resistant to meropenem. These bacteria can colonize the hands of healthcare workers and be transferred to patients, leading to infections that are difficult to treat.Standard and contact precautions, along with emphasis on hand hygiene compliance, are essential [38].

The environment can serve as a reservoir for these bacteria, contributing to the transmission of infections. Implementing effective environmental decontamination strategies can help reduce the risk of infection and limit the spread of resistance. Routine cleaning and disinfection of surfaces and objects in healthcare facilities are essential to remove or inactivate bacteria, including antibiotic-resistant strains. This includes high-touch surfaces such as bedrails, doorknobs, bedside tables, and equipment. Hence,environmental decontamination is an effective control intervention, as MDE can persist on various surfaces for weeks [39].

Multimodal infection control interventions have shown effectiveness in reducing the incidence of carbapenem-resistant Enterobacteriaceae (CRE) and extended-spectrum β-lactamase (ESBL) producers . Early detection through targeted laboratory protocols and comprehensive infection control measures are key to containing the spread of CRE . Proactive and adequate preventive measures are necessary to prevent the establishment of CRE endemicity .

4.4 Public health interventions and policy implications

Public health interventions and scientific policy implications to combat meropenem resistance include the identification of non-synonymous single-nucleotide polymorphisms (nsSNPs) in penicillin-binding proteins (PBPs) that can decrease pneumococcal susceptibility to meropenem [40]. Comprehensive policy assessments using standardized frameworks are needed to evaluate the effectiveness of existing policies, especially in low-income and middle-income countries and in the animal and environmental sectors [41]. Antibiotic stewardship programs (ASP) that involve prospective audit and feedback can improve the adequacy of meropenem prescription and promote de-escalation to narrower-spectrum antibiotics, leading to a decrease in meropenem consumption and hospital-acquired multidrug-resistant bloodstream infections . A robust de-escalation strategy following carbapenem initiation should be encouraged to combat multidrug-resistant organisms [42]. Monitoring antimicrobial usage data, along with resistance data, is crucial for directing education efforts and policy decisions to minimize the risk of antimicrobial-resistant infections in humans.

SUMMARY :

Meropenem resistance is a growing concern in healthcare settings due to its impact on treatment outcomes and limited therapeutic options. Combating meropenem resistance requires a multifaceted approach involving various strategies.

Meropenem resistance has been reported worldwide in various bacterial pathogens, including Enterobacteriaceae (such as Klebsiella pneumoniae and Escherichia coli), Pseudomonas aeruginosa, and Acinetobacter baumannii. The prevalence of meropenem-resistant strains varies across regions and healthcare settings, with higher rates observed in intensive care units and in patients with previous antibiotic exposure.

Several risk factors are associated with the development of meropenem resistance. These include prior exposure to carbapenems, prolonged hospital stays, invasive procedures, presence of indwelling devices, and use of broad-spectrum antibiotics. Immunocompromised patients and those in long-term care facilities are also at higher risk.

Meropenem resistance limits treatment options for serious infections. Infected patients may experience worsening of clinical outcomes, including increased mortality rates and longer hospital stays. The limited availability of effective antibiotics necessitates alternative treatment strategies and the use of combination therapy to improve clinical outcomes.

Strategies to combat meropenem resistance involve multifaceted approaches. These include antibiotic stewardship programs to optimize antibiotic use, surveillance to monitor resistance patterns, infection control measures to prevent transmission, development of new antibiotics with novel mechanisms of action, and the exploration of alternative treatment options. Combination therapy with other antibiotics that inhibit carbapenemases can also restore meropenem activity against resistant bacteria.

5. CONCLUSION

In conclusion , combating meropenem resistance requires a comprehensive approach that includes surveillance, antimicrobial stewardship, infection prevention and control, public education, and research and development. Future research should aim to enhance our understanding of resistance mechanisms, evaluate the effectiveness of interventions, and develop innovative strategies and treatment options to address this urgent public health challenge.

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