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EMERGENCE AND CLINICAL IMPACT OF NDM-1 (NEW DELHI METALLO-Β-LACTAMASE-1) IN *ESCHERICHIA COLI*: MECHANISMS AND THERAPEUTIC CHALLENGES

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ABSTRACT

The increasing lack of effective antibiotics on offer is of particular concern as the resistance of carbapenem can be regarded as one of the most threatening phenomena as carbapenems are often the last resort in most infections. One of the mechanisms of antibiotic resistance that is particularly worrying is the enzyme New Delhi metallo-β-lactamase-1 (NDM-1). As the name implies, this enzyme has great hydrolase activity toward almost all kinds of β-lactam-based antibiotics, including carbapenems. When NDM-1 becomes acquired by the *Escherichia coli* bacteria, which can be said to be the well-known pathogens that cause community- and nosocomial infections, then treating such strains becomes highly challenging, even impossible using common medicines. The following literature review will be based on the course of evolution and propagation of NDM-1 in E. coli and why this is occurring on the molecular level. Meanwhile, it will comment on the clinical implications of such infections and describe some of the promising streams of research that may lead to some progress in this respect in the future. These instructions consist of combination therapy, metal chelating therapy, bacteriophage use, and drug repurposing. In general, the only thing that we need in order to overcome the challenges posed by NDM-1-driven resistance is the invention of new types of treatment and closer collaboration between scientists from various disciplines.

Keywords: Carbapenem, *Escherichia coli*, New Delhi metallo-β-lactamase-1

INTRODUCTION

Antimicrobial resistance (AMR) is one of the most popular in the recent past in the clinical care due to its propensity to be fueled predominantly by the overuse and misuse of antibiotics in clinical, agricultural, and environmental settings. This resistance has been a great challenge to the effectiveness of conventional therapies and has raised the morbidity, mortality and the healthcare expenses around the world.

Escherichia coli is a critical contributor among the many bacterial pathogens because of its dual nature as a commensal organism as well as one of the greatest opportunistic pathogens that cause infections like urinary tract infections, bloodstream infections and gastrointestinal diseases. The rising level of resistant E. coli strains has cast grave doubts about the effectiveness of treatment and control of the infections (Mancuso et al., 2021).

Carbapenems have long been considered as a last-resort antibiotic in the treatment of severe infections by multidrug-resistant Gram-negative bacteria. The development of carbapenem-resistant Enterobacteriaceae has however grossly restricted their clinical use. One of the reasons that led to this resistance is the generation of metallo- bacterial -lactamases and especially New Delhi metallo-bacterial -lactamase-1 (NDM-1), which has spread quickly all over the world since its discovery. Mobile genetic elements (like plasmids) usually carry the blaNDM-1 gene allowing horizontal gene transfer to other bacterial species and enabling a fast expansion (Wu et al., 2022).

The rising prevalence of E. coli that produces NDM-1 is a major public health issue, given the lack of treatment, high morbidity and mortality, extended hospitalization as well as the escalated economic costs. There are no good inhibitors of metallo-2 -lactamases, and the presence of more than one resistance mechanism complicates further, treatment strategies. Hence, knowledge regarding the development, pathophysiology, clinical, and treatment issues of NDM-1 is crucial to the development of effective interventions and informing future studies. (Bush & Bradford, 2020).

Moreover, the increased rate of development of Escherichia coli antimicrobial resistance is directly associated with its genetic flexibility and capacity to obtain resistance determinants via horizontal gene transfer (Martínez et al., 2021). Mobile genetic elements like plasmids, integrons, and transposons are important determinants of diffusion of resistance genes, including blaNDM-1, among different bacterial populations (Bengtsson-Palme et al., 2020). This genetic mobile enhances the spread of resistance in healthcare systems and leads to its sustainability in community and environmental conditions (Nadimpalli et al., 2020). The rising prevalence of NDM-1-carrying strains in wastewater, livestock, and food products indicate complicated routes of transmission and the rising environmental pool of resistance (Hu et al., 2020).

Besides the mechanisms of resistance, the clinical treatment of the NDM-1-producing infections is also complicated by the insufficient diagnostic capacity and therapeutic interventions (Tacconelli et al., 2020). The traditional microbiological procedures frequently do not allow identifying the resistant strains quickly, which results in delays in specific treatment and excessive use of widespread antibiotics (Holmes et al., 2021). This postponement adds to worse clinical outcomes and additional encourages the choice of resistant organisms (Murray et al., 2022). In addition, the economic cost of the long hospital stays, intensive care needs, and expensive treatment highlights the overall healthcare cost of antimicrobial resistance (Dadgostar, 2019).

Emergence and Global Spread of NDM-1

The introduction and fast worldwide dispersion of NDM-1 have had a considerable impact on the antimicrobial resistance crisis. The spread of NDM-1 is mainly due to the mobility of blaNDM-1 gene which is usually found in plasmids that can transfer between bacterial species. This horizontal gene transfer facilitates the quick dissemination of resistance in both clinical and community environments especially among Enterobacteriaceae like *Escherichia coli* (Wu et al., 2022).

Medical tourism, international travel and poor practices in controlling infections have also contributed to the spread of NDM-1-producing bacteria throughout the world. Besides the clinical settings, other environmental reservoirs, including wastewater and surface water have been reported to be important contributors to NDM-1 transmission.

These environments have a high level of antibiotic residues, which provide selective pressure, thereby supporting the survival and propagation of resistant strains. These results demonstrate the significance of the One Health approach that combines human, animal, and environmental health measures in order to positively influence the control of the NDM-1 spread (Khan et al., 2020).

Clinical Impact of NDM-1 Producing *Escherichia coli*

Clinical burden of NDM-1-producing *Escherichia coli* has been on the rise especially in hospital and community health care environments in the past one decade. These strains have been implicated in a broad range of infections, such as urinary tract infections, bacteremia, ventilator-associated pneumonia, and intra-abdominal infections, and typically have severe and acute symptoms. Production of NDM-1 greatly affects the effectiveness of first-line antibiotics, which leads to a delay in the introduction of effective treatment and high risk of failure of therapy (Liu et al., 2020; Dortet et al., 2021).

NDM-1-producing strains exhibit a significant poor clinical outcome of the infections, and in studies, high mortality rates have been reported particularly among critically ill patients and those with immunocompromised patients. Healthcare systems are further burdened by the long hospitalization period and the need to provide an intensive care to the patients. Also, patients with NDM-1-producing E. coli can be asymptomatically colonized, which further contributes to the unrecognized spread in health care institutions, resulting in the ongoing outbreaks. The absence of fast diagnostic systems and standard screening procedures also increase the clinical burden, slowing down the recognition and control of such resistant strains (Rodríguez-Baño et al., 2021; Logan and Weinstein, 2021).

Therapeutic Challenges

Treatment of the infections caused by NDM-1 producing E. coli is very difficult as these organisms have a very wide spectrum of resistance. NDM-1 has been shown to be successful in hydrolysing majority of the β-lactam antibiotics such as carbapenems, and clinicians have limited choices in treatment. Most of the current treatment methods tend to use last-resort antibiotics, including colistin, tigecycline, and fosfomycin, but their application is limited by high toxicity rates, inappropriate pharmacokinetics, and resistance development (Tamma et al., 2021; Paul et al., 2022).

One of the key confounding variables is the fact that there are multiple resistance mechanisms in a bacterial strain. Besides the production of NDM-1, changes in outer membrane porins and expression of efflux pumps also decrease the intracellular concentrations of antibiotics, which further increase the resistance. In addition, there are no clinically useful inhibitors of the metallo-2 -lactamase that would make combinations of 2 -lactams more successful. There are no universally accepted treatment guidelines and the variability of susceptibility patterns across the regions only complicates clinical decision-making. The challenges highlight the importance of new therapeutic agents and treatment regimens that are optimized (Bassetti et al., 2021; Karaiskos and Giamarellou, 2020).

Emerging Therapeutic Strategies

To overcome the shortcomings of existing treatment procedures, a number of new treatment methods are being explored. Combination therapy has demonstrated to be promising, especially those that incorporate aztreonam with ceftazidime-avibactam that is able to bypass the activity of metallo-2-lactamases, but still targets the other 2-lactamases found in the bacteria in the isolate. Such combinations have been shown to have better clinical outcomes than traditional monotherapy (Falcone et al., 2020; Tamma et al., 2021).

One such promising approach has been the use of metal chelation therapy whereby the zinc ions that are required in NDM-1 activity are targeted. The active site of the enzyme can be destabilized by chelating agents which then recovers the activity of the β-lactam antibiotics. Moreover, bacteriophage therapy has become a particularly high-specific and environmentally friendly method of addressing resistance populations due to the ability of bacteria to develop resistance to drugs, and some experimental studies have already proven its effectiveness when used against multidrug-resistant E. coli strains (Gordillo Altamirano & Barr, 2021).

In the recent progress in computational biology, the process of drug repurposing has speeded up, with multiple FDA-approved drugs undergoing molecular docking and simulation analysis and potentially having an inhibitory effect on NDM-1. Moreover, nanotechnology drug delivery systems have been considered to increase the penetration of antibiotics as well as decrease toxicity to achieve better therapeutic outcomes. These new approaches offer promising ways of overcoming NDM-1-mediated resistance and emphasize the role of interdisciplinary research in the fight against antimicrobial resistance (Thakur et al., 2022; Hutchings et al., 2019).

RESULTS AND DISCUSSION

The analysis of molecular biology and structure of E. coli strains capable of producing NDM-1 enzymes show that the increase in carbapenem resistance is majorly due to the the horizontal transfer of genetic material via plasmids. This plasmid mediated gene transfer can occur through both conjunction and transformation. The dynamic regions of genetic structure around the blaNDM-1 gene consist of mobile genetic elements that allow the resistance gene to spread easily contributing to the increase in resistance. The isolated strain that was studied showed resistance to all types of antibiotics used in the experiment, this shows the wide spectrum of hydrolysis of NDM-1 enzymes. The experimental data have shown that NDM-1 genes can be transferred from one bacterium to another using transformation and conjugation methods, which confirms their ability to quickly disseminate. E. coli carries multiple resistance genes which includes β lactamases, this combination creates a multi drug resistant E. coli which is capable of showing resistance to multiple classes of antibiotics at the same time. NDM1 producing E. coli is considered a major health threat globally due to all of these features as it can spread rapidly, and also reduce the efficacy of the strongest antibiotics. (Liu et al., 2013) Through clinical trials a concerning trend was observed towards pan-β-lactam resistance in NDM producing strains of E. coli , even to advanced last resort drugs like carbapenem and almost all β lactam antibiotics which includes penicillins and cephalosporins. The genomic analysis carried out demonstrated that the pan-β-lactam resistance is associated not with a single type of mechanism but rather with the combination of several adaptations. This includes changes in penicillin-binding proteins, disruption of iron transport, pathways, and the acquisition of new β lactamases. Moreover the β-lactamase enzymes such as NDM1 and another enzymes produced by the bacteria breakdown the antibiotics before they have a chance to attack the bacteria which further contributes to the resistance. All these factors work synergistically, due to which the overall effect is far greater than the impact of an individual factor. This makes antibiotics ineffective leading to the failure of the treatment. (Simner et al., 2023) Current advances in the field of therapeutic research show that researchers moved their research toward inhibitor-based therapy, which involves targeting the NDM-1 enzyme directly. Employing computational screening and subsequent experimentation. natural compounds have been discovered, which can inhibit NDM-1 in such a manner as to restore the function of β-lactam antibiotics when combined together. A good example of such a compound is morin, a flavonoid that occurs naturally in plants. Morin alone does not possess strong antibacterial properties, but its combination with the antibiotic drug meropenem exhibits synergy. This implies that morin inhibits NDM-1, and the antibiotic eliminates the bacteria. that the combination of morin and meropenem showed. great improvement in terms of antimicrobial activity, where there was decreased bacterial load and associated tissue damage observed in both in vitro and in vivo models. these results highlight the potential of drug repurposing and rational inhibitors as solutions to NDM-1-based resistance but additional clinical confirmation is needed for practical implementation (Ren et al., 2025)

CONCLUSION AND FUTURE SCOPE

The global increase in the number of infections due to NDM-1 producing E. coli indicates of a major gap between novel drug resistance mechanisms and available effective therapeutics. Recent studies have shown the presence of multiple promising inhibitors of NDM1 which exhibit a high level of synergy when combined with available antibiotics, the process of bringing these inhibitors from lab experiments into clinical and practical application in the clinic is a challenging task. Different types of strategies such as combined therapy, drug repositioning, and enzyme inhibitors, are potential candidates that could become promising solutions if they are facilitated by advances in molecular modelling and mechanism-based research but the limitations associated with issues like safety and efficiency have prevented the use of the strategies clinically. In the future, it is evident that the focus will shift towards the development of safe and effective NDM specific inhibitors, through collaborative scientific studies that combine scientific discoveries with their implementation in clinical practice. Meanwhile, the development of international cooperation in research and an increase in translational research would be crucial in moving forward in this f ield. It is crucial to have a proper strategy along with innovative thoughts for tackling the problem of NDM-1-based resistance in order to sustain the antibiotic resistance management efforts in both the clinical and environmental settings. (Nahar et al,2024).

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