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Review Article

Unveiling carbapenem resistance: mechanism and therapeutic strategies

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ABSTRACT

This review provides an overview of the carbapenem resistance, its underlying causing microbes, its mechanism of transmission, risk factors, and its treatment options and challenges. Carbapenem resistance in Gram-negative organisms such as *E. coli* and *K. pneumoniae*, *S. pneumoniae*, *S. aureus*, *P. aeruginosa*, and *A. baumannii* are major causing microbes. Here we discuss the importance of infection control measures to mitigate the spread of resistance and urgent need for novel therapeutic strategy to defeat this resistance. Furthermore, we explore innovative approaches including the development of new antibiotics, combination therapies and the repurposing of existing drugs to combat carbapenem-resistance strains. Understanding the molecular basis of carbapenem resistance is crucial for developing effective treatment strategies and controlling the spread of antibiotic-resistant bacteria.

Keywords: Centers for accelerating phage, Carbapenem-resistant *A. baumannii*, Carbapenem-resistant *Enterobacterales*, Antimicrobial resistance, Extended-spectrum beta-lactamase, Multidrug resistance, New Delhi metallo-beta-lactamase, Carbapenem-resistant *K. pneumoniae*, Ventilator-associated pneumonia, Bloodstream infections

INTRODUCTION

Carbapenems are one of the last options for treating gram-negative bacterial infections that produce extended-spectrum beta-lactamases. A carbapenem linked to a -lactam ring gives carbapenems their distinctive structure, which affords protection against most-lactamases, including metallo-lactamase (MBL) and extended spectrum-lactamases.[1] Because of their concentration-independent ability to destroy the infecting bacteria, carbapenems are recommended above other antimicrobials when treating invasive or life-threatening illnesses. They have a wide spectrum, acting on both Gram-positive and Gram-negative bacteria, as well as anaerobes.[1] However, the public health concern of carbapenem resistance has risen dramatically.[2] Carbapenem resistance in Gram-negative organisms such as *E. coli* and *K. pneumoniae*, *S. pneumoniae*, *S. aureus*, *P. aeruginosa*, and *A. baumannii*, has thus become a matter of concern globally due to the lack of new alternative treatment options.[3-5] In view of the wide-spread spreading of carbapenenem resistance made possible by carbapenemase, a key component in its transmission, there is an increasing public health concern. There has been horizontal transmission of the carbapenemase gene by conjugative plasmids, transposons, and insertion sequences.[2]

CARBAPENEM ANTIMICROBIALS

Carbapenems have been used as antibiotics of last resort against Gram-positive, Gram-negative, and anaerobic bacteria.[6,7] In hospitals, intravenous administration of carbapenem drugs is done with minimal to no allergic

cross reactions.[1] As a result of the increasing cephalosporin antimicrobial resistance in the *Enterobacteriaceae* family, carbapenems, such as imipenem, doripenem, biapenem, meropenem, and biapenem, have been utilised often in hospital acquired infections.[1-7] These carbapenems are usually given only to patients who have multi-drug resistant (MDR) bacteria, which include those that cause complex urinary and intra-abdominal infections, meningitis, and febrile pneumonia, bloodstream and skin infections, community-acquired and nosocomial pneumonia.[7-9] These infections can also be caused by bacteria that produce ampicillinase C enzyme and extended spectrum-lactamase (ESBL) enzyme.[7-10]

MOLECULAR AND TRANSMISSION MECHANISM OF CARBAPENEM RESISTANCE GENES

The best initial step to directing the treatment of CAPT-resistant gramme negative bacteria is understanding the molecular basis of resistance to carbapenems. Carbapenem resistance can be caused by a number of methods:[12] Porin mutation resulting in decreased permeability of the outer membrane. The cell walls' efflux pumps are turned on to eliminate the antibiotics that are taken up by the cell. By the production of carbapenemases. By modifying the antibiotic's targets so that they can no longer bind to them via altering intracellular enzymes (target modification).[13] A new cell process being created to get around the antibiotic's effects.[7-14] They are mostly propagated via plasmid acquisition or other mobile components, permeability changes brought on by porin loss, and an overexpressed efflux mechanism.[16]

There are three main ways that genetic material is transferred between bacteria: Transformation, the chromosome's acquisition of free DNA from the environment; viral particles are used in transduction, a process by which phage's transfer DNA from infected cells; and transferring plasmids from one bacterium to another by conjugation. Conjugation is the most effective and frequent method of exchanging genetic information. Because it always leaves a replicate of the resistant gene behind, it causes AMR to develop and transmit.[7]

GROUPS AT RISK FOR DEVELOPING CARBAPENEM RESISTANCE

One cause of the elevated level of antimicrobial resistance in underdeveloped nations is the scarcity of antibiotics; this issue is made worse by the fact that inadequate antibiotic substitutes are currently being developed. mainly due to the lack of financial incentive for the development of novel antimicrobial medicines, the inadequate accessibility, affordability, availability, and quality of antibiotic agents lead to the development of AMR. Additionally, in low-middle income nations where antibiotics remain available without a prescription from a doctor, self-treatment with antibiotic agents is frequent, although they cannot legally be sold without a prescription from a physician according to the health authorities.[3,17]

According to the current study, the use of devices-particularly implants introduced during medical care, increased the risk of infection by nearly four times for bacteria that produce MBL and carbapenemase. These were the extra significant factors linked to bloodstream infections that are resistant to carbapenem.[18] Previous research has also shown that the air, high-density electroencephalogram material, Velcro on blood pressure cuffs, medical instruments, furniture, and gloves are all potential sources of cross-contamination for multi-drug-resistant bacteria, specifically CRAB in ICUs. Suction machines, drainage tubes and intravenous lines, were among the medical devices linked to bacterial infections that produced carbapenemase and MBL, so it is important to monitor the sterilisation of surgical supplies and indwelling medical devices during treatment.[18] The abuse of antibiotics in animals used for food production has also been noted as a significant contributor to antibiotic resistance.[2]

Meropenem (11%), co-amoxiclav (9%), and piperacillin/tazobactam (9%) with 30% of patients receiving multiple drugs, were the most commonly used empirical antibiotics to treat the index infection. This trend of prescribing highlights the goal for regular, broad distribution of potential multidrug resistance GNB, such as ESBL, while additionally taking into account additional factors such as the degree of sickness and the presence of risk factors for resistant infection.[20]

PATIENTS WITH CARBAPENEM RESISTANCE INFECTIONS IN ICUS

With a rise in hospital stay time and expenses, particularly for patients referred to ICUs, CRAB infection has a mortality rate of up to 70-80%.[21] About 55% of CRAB infections involve the respiratory system.[22] It typically manifests as ventilator-associated pneumonia (VAP) and develops slowly while a patient is being treated in an intensive care unit (ICU). The majority of cases affect people who have already been colonised. In contrast to patients who acquire VAP from other gram-negative bacilli, individuals with VAP caused by CRAB require prolonged breathing and spend longer in the ICU.[22]

PREVENTION AND CONTROL

In order to prevent cross-infection, ventilator use should receive more attention than other wards when lung infection caused by CRAB occurs in ICUs. However, independent risk factors for CRAB-caused lung infections have been established that go beyond use of mechanical ventilation, such as prior hospital visits, extended stays in intensive care unit, and prior carbapenem use.[19]

Patients with colonisation and infection must be kept apart from recently admitted patients, and each group should get treatment from another member of the medical team. The possibility of transmission and infection is also reduced by sufficient environmental cleaning and disinfection. Effectively lowering the incidence of CRAB in ICUs is short-term carbapenem restriction.[19] The spread of such a highly resistant strain is thought to have been stopped by the implementation of strict infection control protocols, such as strict patient cohorts, the appropriate selection of treatment methods, and the use of colistin as the final treatment option.[23] However, obtaining an infection that is resistant, like CRE, can result in patients having to stay in hospitals for a longer period of time. Therefore, keeping up strong infection prevention practises is essential for lowering transmission rates. In order to prevent VAP, medical staff members are necessary to provide a sterile environment by avoiding bodily fluid contamination, utilising sterile equipment and safe injection techniques, and maintaining respiratory hygiene.[23]

If an indwelling device is present, it should be replaced if at all possible and no further treatment is required if there are no indications of an ongoing infection. Devices should be updated or removed and patients should receive treatment if there are indications of a current infection. It is usual practise for patients receiving care in intensive care units to have urine catheters implanted. These patients' urine cultures are commonly positive. However, unless there are obvious symptoms of infection of the urinary source, the majority of positive cultures in the urine of such patients represent colonisation and do not necessitate therapy.[22]

CARBAPENEM RESISTANCE CAUSING MICROBES

Enterococcus spp.

E. coli is primarily responsible for community-associated infections, making the implementation of standard preventive strategies based on infections acquired in hospitals difficult. Similar to other bacteria, *E. Coli* can cause bloodstream, lung, and urine infections in people with weakened immune systems.[2] The best option for the management of nosocomial *E. coli* infections was once more carbapenem. However, the emergence of carbapenem-resistant *E. coli* was mostly due to the synthesis of carbapenemases, as well as a reduction in antibiotic permeability (increased efflux pump and absence of porin) and a change in the carbapenem binding sites.[23] *Enterobacter* spp. with plasmid-borne ESBLs and carbapenemases have been related to serious hospital acquired infections, therefore this pathogen is now a developing concern.[24] Various medication resistance in addition to having essential resistance genes (blaNDM, blaCTX-M group 1 and blaOXA) that are of concern for drug-resistance among *Enterobacter* spp., were resistant to important types of antibiotics (cephem, -lactam inhibitor, 5'fuoroquinolone and aminoglycoside, carbapenem.).[4]

K. pneumoniae

K. pneumoniae is a non-motile gram-negative organism that colonises the human digestive and respiratory systems and might infect immunosuppressed hosts. Although it is currently unknown how gut colonised *K. pneumoniae* penetrates the intestinal barrier, it is one of the major bacteria responsible for 10% of nosocomial infections.[25-27] Several-lactamase enzymes, which hydrolyze-lactam medicines such penicillins, cephalosporins, and carbapenems, have been acquired by several K. pneumoniae in recent years. The development of NDM-1, encoded by blaNDM-1, in *K. pneumoniae* has led to a rise in the number of isolates that have this gene.[4] *K. pneumoniae* and other gram-negative bacteria, as well as *Enterobacteriaceae*, carry carbapenemase genes that are primarily located on plasmids.[27]

A. baumannii

A. baumannii, a gram-negative, aerobic *Coccobacillus* species. The colonisation of the gastrointestinal tract with *A. baumannii* in patients in intensive care units is a significant risk factor for the emergence of antibiotic resistance, increasing the severity of the illness and serving as a vital reservoir for clinical infections and hospital outbreaks.[28] Due to its widespread distribution, the dearth of efficient treatments, and the high mortality rates, carbapenem-resistant *A. baumannii* (CRAB) is classified as a "urgent threat" by the centre for disease control and prevention.[29] *Acinetobacter* infections have a high mortality rate that can range from 45 to 70%.[22] Carbapenems, cephalosporins, monobactams, -lactam inhibitors, and 5-fuoroquinilones were all effective against more than 94% of *A. baumannii*[4] Infections caused by *A. baumannii*, such as pneumonia, meningitis, wound and surgical site infections, and urinary tract infections, are highly difficult to treat. Infections are more frequent in populations that are critically ill or immunocompromised, and this difficulty is worsened by the organism's widespread MDR and the rapidly diminishing number of available treatments.[5] The primary mechanism of carbapenem resistance in *A. baumannii* is the production of class D carbapenemases, with OXA-23 being by far the most common across most nations, and less frequently class A (including KPC and GES) and class B (MBL) carbapenemases.[13]

P. aeruginosa

Many hospital-acquired infections are caused by *P. aeruginosa*, particularly in elderly or immunocompromised individuals. *P. aeruginosa* has been reported to be the cause of 10-20% of infections among hospitalised patients.[30] Due to their strong inherent resistance to numerous antimicrobial drugs, such as

cephem and -lactam inhibitors, *P. aeruginosa* continue to be problematic. However, the presence of blaNDM-1 in these isolates is worrying.[4] Resistance was brought about by modifications in porin expression, which prevented imipenem from penetrating the outer bacterial membrane. Although meropenem exhibits less of this resistance mechanism than other drugs, Increased efflux pump activity can make *P. aeruginosa* resistant to meropenem.[31]

TREATMENT OPTIONS

There are currently very few antibiotic choices for treating CRE. The standard therapies include polymyxin, fosfomycin, tigecycline, and aminoglycosides.[32,33] Additionally, a number of therapeutic approaches, such as the use of high doses of antibiotics, double carbapenems, and combination antibiotics, are utilised to treat severe CRE infections in order to maximise the efficacy of treatment.[33-35]

Colistin

Colistin is a polymyxin-based antibacterial agent. Polymyxin E is the most popular form. It effectively combats CRAB, *P. aeruginosa*, and *A. baumannii* among other Gram-negative bacteria.[36,37] Bactericidal action is concentration-dependent.[38] Early in the course of an infection, colistin requires a while to reach an effective concentration; it needs at least two days for the drug to reach steady-state levels without providing a loading dose.[38] This medication used to be used sparingly due to its nephrotoxicity side effect, but recently it has gained popularity as a last-line of protection against Gram-negative bacteria that are resistant to carbapenems. One of the most prevalent and harmful side effects of colistin treatment for patients is nephrotoxicity.[37] Furthermore, according to those investigations colistin-induced nephrotoxicity appeared to be dose-dependent.[37-39] When colistin is taken, careful monitoring of renal function is strongly advised.[19]

Polymyxin B

Polymyxin B and colistin methate/colistin differ pharmacologically in a number of ways, including the fact that polymyxin B is administered in an active form and that its clearance is not dependent on renal function. Therefore, in patients with high Clcr (>80 mL/min), it is possible to achieve appropriate exposure more quickly and consistently with it than with colistin m methate/colistin. Additionally, the treatment window is significantly reduced by polymyxin nephrotoxicity, one of its major drawbacks.[38]

Aminoglycoside

Aminoglycoside monotherapy or combination regimens have been demonstrated to be effective against CRKP in in vitro experiments. Aminoglycosides have a limited role in treating infections in the lungs and abdomen due to their high risk of side effects such nephrotoxicity and ototoxicity and their comparatively weak penetration into those areas.[40]

Rifampicin

The bacterial ribonucleic acid (RNA) polymerase is inhibited by rifamycin antibiotics, including rifampin, rifabutin, and rifapentine.[22] Colistin-resistant *Acinetobacter baumannii* postsurgical meningitis and colistin-resistant *Acinetobacter baumannii* pneumonia have both been successfully treated with the combination of colistin and rifampicin.[13]

Tigecycline

Tigecycline, the first compound of the glycylcycline class, is a minocycline analogue.[13] Tigecycline exhibits desirable activity against MDR bacteria except for *P. aeruginosa* and *Proteus* spp. When additional potent antibiotic options are available, tigecycline generally shouldn't be administered as a sole agent.[13] Combination antimicrobial therapy according to TGC was not more effective than monotherapy.[19] Although tigecycline is frequently used to treat CRAB infections, usually in combination with other drugs, its effectiveness is still up for debate. The main drawback of tigecycline is that it has unfavourable pharmacokinetics in the blood and the lung, which are the two most typical areas of Acinetobacter infection.[38] As cases with a drop in plasma fibrinogen concentration and severe coagulopathy have been documented, the high-dose regimen of tigecycline should be used with close toxicity monitoring.[38] Tigecycline is effective against the majority of CRE, *A. baumannii*, and *S. maltophilia* strains among gram-negative organisms that are resistant to carbapenems.[31] Due to its bacteriostatic action and low steady-state serum concentrations at the appropriate dosage, tigecycline is typically not advised for bacteremia.[31,41] It has no effect on *P. aeruginosa* and is less effective than tigecycline against CRE.[31]

Fosfomycin

Fosfomycin can also be utilised for various conditions in addition to treating simple urinary tract infections.[22] Fosfomycin is efficacious against the majority of carbapenem-and CRE-resistant *P. aeruginosa* strains, but is ineffective against *A. baumannii* or *S. maltophilia* strains, according to the current susceptibility limit for urinary tract isolates.[31,42]

Eravacycline

Antibiotics from the tetracycline class, such as eravacyline, have been approved for the treatment of challenging intra-abdominal infections.[22] Eravacycline is active against gram-negative bacteria such as CRE, *A. baumannii* and *S. maltophilia* carbapenem-resistant

strains, but not *P. aeruginosa*.[31,43] It is also effective against numerous clinically important anaerobic species and gram-positive bacteria, such as methicillin-resistant *S. aureus* and vancomycin-resistant *enterococci*.[31,44]

Aztreonam

The monobactam antibiotic family includes aztreonam, which is resistant to OXA-48 enzymes and metallo-beta-lactamase (MBL) activity but is degraded by serine-lactamases.[45] Aztreonam-avibactam is being developed for treatment against infections brought on by carbapenem-resistant *Enterobacterales*, including isolates containing MBL.[45,46] Infections brought on by MBL-producing MDR and XDR *Enterobacterales* may benefit from therapy with aztreonam-avibactam.[47]

COMBINATIONS VERSUS MONOTHERAPY

In nations where these drugs are now accessible for clinical usage, ceftazidime-avibactam, meropenem-vaborbactam, and ceftolozane-tazobactam for carbapenem-resistant *P. aeruginosa* infections have lately emerged as crucial treatment alternatives.[31] Combination therapy is effective in treating a variety of complicated infectious disorders. Combination therapy has been proved to improve treatment outcomes but also raises the risk of adverse events and death.[48] Meropenem-vaborbactam and imipenem-relebactam are two specific combination medicines that have been licenced, while others, such aztreonam-avibactam, are still in the research and development stage.[48,49] The idea behind this combination is that ertapenem functions as a suicide inhibitor because of its increased affinity for the carbapenemase enzyme, enabling higher levels of the second carbapenem (usually meropenem or doripenem).[13,50] Plazomicin, cefiderocol, and eravacycline are a few other drugs that have recently received approval and have been used for CRE.[48,19]

Colistin combination regimens have been suggested as a way to combat bacterial regrowth following colistin monotherapy, either by lowering resistance or by improving bacterial killing through a synergistic action of 2 antimicrobials. By acting concurrently, sub-populations or mechanistic synergy can have a better antibacterial impact.[51] Combination of polymyxin/ meropenem and polymyxin/ rifampicin against *A. baumannii* isolates shown a high level of synergy, according to a systematic review and meta-analysis that simply included killing assay (PK/PD and time-killing) studies.[51,52] Colistin and daptomycin work 100% synergistically to effectively combat our CoR *A. baumannii* strains.[51]

Ceftazidime/avibactam, ceftolozane/tazobactam, imipenem/relebactam, aztreonam/avibactam and meropenem/vaborbactam, are all ineffective against carbapenem-resistant *A. baumannii*.[13-24] Another potential combination that has been used successfully to treat CAPT-resistant *A. baumannii* VAP is ampicillin-sulbactam coupled with meropenem and polymyxins.[13] A recent multi-center observational analysis found that compared to other active treatments for bloodstream infection by MBL-producing *Enterobacterales*, the combination of ceftazidime/avibactam and aztreonam was associated with considerably decreased clinical failure, death, and duration of stay (predominantly *K. pneumoniae*).[13,53]

We advise administering two active medicines in combination to neutropenic individuals since monotherapy with polymyxins or aminoglycosides has a high failure rate. Recent research indicates that there is no additional advantage to colistin dual therapy over colistin monotherapy.[22]

DISCUSSION

Acinetobacter spp., *K. pneumoniae*, and *K. oxytoca* were the three most prevalent bacteria that produced several drug hydrolyzing enzymes. This suggests that *K. pneumoniae, K. oxytoca, E. coli, Acinetobacter* spp., and other aggressive drug-resistant bacteria were developing. Additionally, possessing several drug-hydrolyzing enzymes makes it simpler for bacteria to resist antibiotic treatment, which raises the failure rates of treatment, lengthens hospital stays, increases the economic burden, on patients, and incurs unexpected psychological expenses.[18]

The physicians' specialties had an impact on the decision about empirical treatment for CRE infection. The majority of internal medicine practitioners could prescribe in accordance with the recommended antibiotic treatment guidelines.[35] Culture reports, site of infection, MIC, pharmacokinetics and pharmacodynamics, disease state, and patient clinical manifestations were other criteria that went into choosing antibiotics for particular therapies and were also documented in the literature.[35,54]

Unsuitable CRE treatment is frequently used as a result of the challenge in treating CRE infection. Additionally, ineffective particular antibiotic treatment, such as the use of non-coverage antibiotics and a delay of coverage medicines, is linked to subpar clinical results for the treatment of CRE.[22,35] 'Severe' HAP, VAP, and BSIs with sepsis and septic shock (severe CRAB infections). We suggest using a combination of two in vitro-active drugs to treat these infections; these drugs may include high doses of ampicilline-sulbactam, polymyxins, aminoglycosides, tigecycline, and minocycline. Combinations of polymyxins with aminoglycosides should be avoided due to increased nephrotoxicity. When choosing the best targeted combination scheme, in vitro synergy studies may be used as a backup plan if two active medicines are not readily available.[38] The spread of CPE isolates is a significant issue since these infections call for fast and extended antibiotic treatment, increasing the risk of side effects and extending hospital stays.[2]

Colistin is given as the prodrug colisimethate (CMS), which must be hydrolyzed to become the active ingredient. The majority of CMS is eliminated in the urine (70%) and is only minimally removed by the kidneys (1-2%). CMS is also partially converted to the active form of colistin (30%). CMS will be converted to colistin to a greater and greater extent as renal function declines. It is therefore difficult to administer colistin at the proper dosage. The loading dose (LD) of CMS is strongly advised when CMS is administered to patients, especially those who are critically ill, in order to increase the serum concentration of the drug quickly.[36,37] Furthermore, dose dependence of colistin-induced nephrotoxicity was observed.[37]

Combination treatment has been proposed to increase the probability of effective empirical antibiotic coverage prior to the knowledge of drug susceptibility test results, hence avoiding multiple mechanisms of resistance, reducing the risk of emerging resistance, and enhancing clinical outcomes.[6] The fact that CRAB-infected susceptible and critically sick patients are frequently recommended combination therapies that comprise carbapenem, polymyxin B, and/or ampicillin-sulbactam was not surprising.[56,57] The use of non-beta-lactam betalactamase inhibitors like avibactam, relebactam, and vaborbactam as treatments for CRAB appears to be ineffective.[22] Furthermore, when compared to colistin alone (42.9-57.4%), the incidence of 28-day death was not decreased by therapy with combinations of colistin with rifampicin, Fosfomycin, meropenem (42-52.2%).[58] Many clinicians are hesitant to administer polymyxin monotherapy to critically ill patients who have hospital-acquired or ventilator-associated pneumonia (HAP/VAP) or bacteremia because polymyxins are unable to effectively reach the PK/PD targets in a number of infections, and because doing so proceeds the risk of selecting for resistance during therapy.[38] The most effective treatment is a regimen combining rifampin and meropenem colistin. According to data, this combination was bactericidal and had a synergistic effect on the carbapenemase enzymes that are produced by *K. pneumoniae*.[45] Methicillin-resistant *S. aureus* can still be treated with glycopeptides and daptomycin, but treatment options for Gram-negative bacilli that produce carbapenemases are severely reduced. Gram-negative bacteria that produce carbapenemase are highly resistant to all beta-lactam antibiotics, or almost all of them, and frequently carry additional genes for fluoroquinolone and/or aminoglycoside resistance mechanisms.[3] Eravacycline is more effective than tigecycline and may be effective against some strains that are tigecycline-resistant.[13]

Early detection of CPE and distinguishing between CPE and non-CPE result in better clinical results as well as time and money savings in an environment where the prevalence of carbapenemases is rising.[3] Phenotypic approaches are efficient and trustworthy for common clinical usage, especially within developing nations, as opposed to PCR-based approaches, which are expensive, time-consuming, and unable to discover novel unidentified genes.[3] To ensure the efficacy of treatment, the frequent isolation of CRAB in ICUs demands precise antibiotic susceptibility testing (AST), particularly to colistin. In order to effectively use AST when using colistin, medication concentration monitoring and careful administration are essential.[19]

Accurate antibiotic susceptibility testing (AST), especially for colistin, is needed due to a higher incidence of CRAB isolation in ICUs in order to ensure effective treatment. As a result, when using colistin as a treatment, medication concentration monitoring and precise usage of AST are essential.[19]

CONCLUSION

Modern rapid phenotypic and genotypic techniques frequently call for expensive, advanced technology, trained staff, and pristine cultures. Both conventional and immunological biosensor assays provide quick and affordable detection, but they still need complex techniques for signal interpretation and measurement. Understanding the molecular basis of carbapenem resistance is crucial for developing effective treatment strategies and controlling the spread of antibiotic- resistant bacteria.

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