# Combatting Carbapenem Resistant Enterobacteriaceae: A Review on Infection Control Measures in Hospitals, Outbreak Management, Challenges and Barriers

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## Abstract

The resistance of carbapenem medicines by carbapenem resistant Enterobacteriaceae (CRE) has come to pose as a huge threat to world healthcare because the drugs are sometimes used as the last form of defense against multidrug-resistant infections. Severe morbidity and mortality, extended hospitalizations, and increased healthcare spending have been linked to infections by CRE. This review elaborates a mechanism of resistance, epidemiology, infection prevention measures, issues, and promising new strategies in controlling CRE in health-care facilities. CRE

outbreaks can be managed with the aid of infection control methods, which include antimicrobial stewardship, environmental cleaning, active surveillance, and contact restrictions. Likewise, resources, health care personnel' knowledge gaps, and the rapidly changing mechanism of resistance would be the other areas that need to be addressed. New infection prevention techniques were developed on the foundation of innovations like probiotic integration, real-time analytics, and genomic surveillance. This article highlights the understanding of molecular processes and regional epidemiology of Enterobacteriaceae which are involved in the development of strategies to fight health problem globally.

**Keywords:** Enterobacteriaceae, Carbapenems, CRE, Resistance, Epidemiology, Infection measures, Hospitalizations, Health-care facilities.

## 1. Introduction

The family of Enterobacteriaceae has evolved into an impermeable resistance to carbapenems, which are the last lines of medicines for combating multidrug-resistant infections. Due to its nature of causing more dangerous infections, which were once considered nearly impossible to be treated, CRE emerged as a grave health concern in the global community, where morbidity and mortality levels were on the higher scale. CRE infections are very common in healthcare, spreading widely among patients who happen to have low immunity or are undergoing invasive medical procedures (Ojo et al., 2020; Shi, 2021; Musa, 2023).The primary thing that causes CRE resistance is the production of carbapenemase, which stops carbapenem antibiotics and beta-lactam antibiotics in general from working (Ojo et al., 2020; "undefined," 2019). Such resistance not only complicates treatment but also increases the failure rate and leads to other adverse outcomes.

Research generally indicates that CRE infections have significantly higher case fatalities than CSE infections (Martin et al., 2018; Yoshida et al., 2022). Sheu et al. (2019) regard CRE as a priority pathogen that requires urgent improvement, emphasizing strengthening the surveillance system and reducing its spread rate. The high rates of transmission in healthcare facilities further compound the threat of CRE and lead to outbreaks that can easily overwhelm health care systems (Musa, 2023; Marusinec, 2024). The rising rate of CRE is ascribed to factors such as the misapplication and overuse of antibiotics, weak infection control measures, and a deficiency of adequate diagnostic techniques to detect the resistant strain (Lovison et al., 2020; Thaden et al., 2016). Besides this, a lack of newly active antibiotics against CRE creates infections with these bacteria quite tough to tackle (Sheu et al., 2019; Thaden et al., 2016). Effective utilization of antibiotics, proper infection control measures, and new research avenues to develop further treatment options have been necessitated for tackling the challenges of CRE (Ghafur et al., 2012; Zequinão et al., 2020; Rajni et al., 2018). Improvement in infection control and antibiotic use needs to be enhanced.

The mechanism of resistance, high rate of transmission, and morbidity as well as mortality that accompanies make it a challenge to the public health sector in this world. Across all global health institutions, CRE was categorized as a priority pathogen in need of urgent strategies against the causative agent. Carbapenem-resistant Enterobacteriaceae (CRE) have significant impacts on

health care environments because they make patient care more challenging, increase healthcare costs, and raise the risk of poor patient outcomes. The emergence and spread of CRE have brought about increased challenges to infection control. This leads to a significant need for strong monitoring and intervention systems in health care facilities. The first critical impact of CRE on health care is an increased morbidity and mortality associated with infections by these resistant organisms. There are various studies that have suggested that mortality in patients infected with CRE is higher than those infected with carbapenem-susceptible Enterobacteriaceae (Ling et al., 2015; Conlan et al., 2014). Treatment issues for CRE infections frequently lead to prolonged lengths of stay in the hospitals, expensive healthcare costs, and utilization of health services (Schechner et al., 2011; Haytolu et al., 2020). Patients who are colonized by CRE have a higher chance of developing subsequent infections. For patients in this category, sometimes critical complications may emerge when the patients are immunocompromised (Wangchinda et al., 2022). Infection control practices provide a means of averting the spread of CRE infection in health facilities. Some effective interventions are based on risk-based screening, cohorting patients, and hand hygiene policies by healthcare workers (Schechner et al., 2011; Chang et al., 2021).

Furthermore, stewardship programs of antimicrobials are crucial in eliminating inappropriate use of antibiotics, which causes resistance (Lee et al., 2023). For instance, those hospitals that have established proper surveillance and prevention programs show fewer cases of transmission of CRE as evidence that implemented infection control interventions work well (Brennan et al., 2014; Rizzo et al., 2019). A CRE infection in the healthcare setting also prevents normal hospital operations. When a CRE infection leads to a breakout, hospitals must isolate infected patients and utilize more personal protective equipment and staff for infection control practices (Park et al., 2023). This stretches the resources of the hospitals and impacts the quality of care offered to all patients. Healthcare professionals may experience stress and burnout due to the complexity of managing resistant infections (Patel & Bonomo, 2013).

## 2. Epidemiology of CRE

The growing problem of emerging global health issues, which are found in varying degrees of prevalence within regions and countries, is due to the production of carbapenemase by CRE-the antibiotic-resistant bacterium. This enzyme confers resistance against carbapenem antibiotics on the bacteria themselves. The infection is then difficult to treat because of the resistance. The risk of severe infections also increases due to the presence of resistance. Studies have proven that CRE has been reported to have very low rates, up to 29.8% around the globe, depending on the area studied, and in certain epidemic areas, it was even reported as high as quoted by Premanadham et al. in the year 2022. The prevalence rate of CRE was estimated to vary differently across the various cities of India, reportedly at the higher level of 71.25% in Mumbai followed by that of 12.26% in Delhi and 7.87% in Chandigarh, respectively (Premanadham et al., 2022).

That may be due to differences in infection control practices and differences in the performance of antimicrobial stewardship programs across these facilities, respectively (Premanadham et al.,

2022; Dinkarrao, 2023). It is alarming in Southeast Asia, where it is reported at 70.5% to 91% in countries such as Singapore and Thailand (Suwantarat & Carroll, 2016). Its dissemination of NDM-type metallo-β-lactamases was especially prominent in this region as part of the reason for high prevalence of carbapenem-resistant Klebsiella pneumoniae and Acinetobacter baumannii (Curcio, 2013). A cross-sectional study in Nigeria recorded a prevalence of 22% among Enterobacteriaceae isolates, an alarming trend in West Africa, according to Adesanya & Igwe, 2020.

The CDC classifies CRE as an emerging and urgent threat in the United States. Estimated hospitalizations from infections range between 2.7 and 3.1 million annually (Yoshida et al., 2022). The prevalence of specific carbapenemase genes like bla KPC varies immensely, from a reported general population prevalence rate of 0.5% up to 38% prevalence in some hospitals in Brooklyn (Shanmugam et al., 2013). This again focuses on the importance of local epidemiological data in understanding how CRE is distributed. These aspects make the global landscape of CRE more complex since they can acquire and disseminate resistance genes between species using plasmids (Abe et al., 2019). Horizontal gene transfer is claimed to be responsible for fast spread of CRE in the healthcare settings, thus implying that there is a need for stringent surveillance and infection control measures to curb their influence (Ghafur et al., 2012; Carrilho et al., 2016).

## 3. Mechanisms of Carbapenem Resistance

Carbapenem resistance among bacteria, especially among Enterobacteriaceae and Pseudomonas aeruginosa, are among the major threats that have become a menace to public health in the production of several mechanisms, among them carbapenemases. Carbapenemases include KPC, which is Klebsiella pneumoniae carbapenemase; NDM, which is New Delhi metallo-β-lactamase; and VIM, which is the Verona integron-encoded metallo-β-lactamase, among others. Carbapenemases have been known to play a significant role in the mechanisms through which these pathogens show resistance to carbapenems. These are antibiotics that are often considered to be the last line to use in treating severe infections. The mechanisms of carbapenem resistance are complicated and multifactorial. In its use, the predominant mechanism is the production of carbapenemases, which hydrolyze the β-lactam ring, thereby making the carbapenems ineffective. For example, it has been well established that the blaKPC gene is highly prevalent in the Klebsiella pneumoniae strains that produce resistance to carbapenems. On the other hand, blaNDM and blaVIM are more commonly found in Pseudomonas aeruginosa and in Enterobacteriaceae (Abdalhamid et al., 2016; Lee et al., 2021).

The genes are typically associated with mobile genetic elements like plasmids and transposons; they facilitate horizontal gene transfer among bacterial populations (Gong et al., 2018, Zaman et al., 2018). This mobility complicates treatment options by allowing fast spreading of resistance traits within different strains and species, as illustrated in Manyahi et al., 2022. There are more mechanisms that contribute to carbapenem resistance than the synthesis of carbapenem. For example, OprD porin loss in Pseudomonas aeruginosa that is due to changes in outer membrane proteins has been associated with very significantly reduced carbapenem uptake (Abouelfetouh

et al., 2019; Lai et al., 2018). Increased efflux pumps, such as the AdeB efflux pump, have also been recognized as mechanisms that increase resistance by actively pumping antibiotics out of the bacterial cell (Dogonchi et al., 2018). These mechanisms can also act synergistically or autonomously and, hence, have a compounded effect on the resistance levels. Moreover, expression and impact of resistance genes are also impacted by their genetic environment.

**Table 1:** Key Mechanisms of Carbapenem Resistance.

| Mechanism | Description | Examples | References |
|---|---|---|---|
| Carbapenemase Production | Enzymes that hydrolyze the β-lactam ring, rendering carbapenems ineffective. | KPC, NDM, VIM | (Abdalhamid et al., 2016; Lee et al., 2021) |
| Porin Alterations | Changes in outer membrane proteins reduce antibiotic absorption. | Loss of OprD in Pseudomonas aeruginosa | (Abouelfetouh et al., 2019; Lai et al., 2018) |
| Efflux Pumps | Active expulsion of antibiotics from bacterial cells. | AdeB Efflux Pump | (Dogonchi et al., 2018) |
| Horizontal Gene Transfer | Transfer of resistance genes via plasmids and transposons. | blaNDM, blaKPC | (Gong et al., 2018; Zaman et al., 2018) |

It has been reported that insertion sequences that enhance the expression of the blaNDM-1 gene besides enhancing its stability in the genome of bacteria generally determine the genetic environment of the gene (Zaman et al., 2018). Similarly, the presence of other resistance genes, for example, aminoglycosides and fluoroquinolones, can enhance the resistance phenotype exhibited among clinical isolates (Yamada & Suwabe, 2013). Other factors include the widespread use of carbapenems in clinics and failure to institute strict infection control measures (Peng et al., 2019; El-Mahdy & El-Kannishy, 2019). Their use of antibiotics is so rampant that resistant strains are favored to cause outbreaks in healthcare institutions (Majlander et al., 2021). The environmental reservoirs' resistance genes spread through food, animals, and other mechanisms, which pose a great risk to public health (Okello, 2023).In a nutshell, carbapenem resistance is mediated through several complex molecular mechanisms due to the production of carbapenemases, modifications in the porin channels, the activity of efflux pumps, and mediation by mobile genetic elements. Therefore, it is very crucial to know this for the purpose of developing an effective combating strategy against the emergence of carbapenem-resistant infections. Infection Control Measures Carbapenem-resistant Enterobacteriaceae, or CRE, spread in hospitals and healthcare facilities is one of the challenges to infection control efforts. Appropriate infection control is essential to prevent the spreading of the multiresistant organisms.

A number of recent synthesized studies outline a few salient strategies that have been proven effective for mitigating CRE spread in healthcare facilities. Among the most effective measures is strict contact precautions, such as using PPE that includes gloves and gowns among the health workers interacting with a patient known or suspected to be colonized with CRE. Loon et al. (2018), Epson et al., 2014). Cohorting also involves the placement of patients with CRE as well as those at risk of colonization in the same setting to reduce cross-transmission and

contamination within the healthcare facility (Mularoni et al., 2019; Gohil et al., 2017). This also limits the spread and puts the affected patients under strict monitoring and management. Another key component of infection control is active surveillance for CRE. Routine screening of patients within settings that are risky, for example, within ICUs and long-term care settings, easily detects colonized or infected patients (Ling et al., 2015; Guh et al., 2014). It is with this need in mind to prevent epidemics and place timely isolations. Furthermore, understanding local epidemiology would make it easier to modify screening procedures in accordance with the prevalence and particular risk factors of CRE in a particular hospital context (Park et al., 2023). Antimicrobial stewardship programs represent an important control mechanism on the emergence and spread of CRE. Optimization of the use of antibiotics helps relieve selective pressure that could perpetuate resistant strains (Nair & Vaz, 2013; Decraene et al., 2018). Restriction of the use of carbapenems apart, stewardship also means proper use of other antibiotics that might contribute to the emergence of resistance. It is also highly dependent on the knowledge and training of health staff to effectively control infection.

If all the healthcare personnel know the infection prevention procedure, which includes PPE use and good hand hygiene, the spread can be very much stopped (Park et al., 2023; Sakai et al., 2021). And as far as high-turnover settings are concerned, this applies even more. For instance, some of the care settings that may not prepare their caregivers well in terms of infection control include long-term care facilities (Park et al., 2023). Also, there is strict environmental cleaning and disinfection procedures especially in areas where patient care was found with CRE. This includes cleaning surfaces and equipment regularly as well as monitoring for the presence of environmental reservoirs of CRE to prevent reinfection and further spread (Decraene et al., 2018, Kanamori et al., 2017). Lastly, a holistic approach to controlling CRE calls for collaboration between health facilities within a given region. More effective efforts on the facility level can be made if epidemic information is disseminated, and regional infection control practices are enforced according to what Guh et al. (2014), and Kanamori et al. (2017) note. All of these measures constitute a multiple approach towards stopping CRE within hospitals. They vary in intensity ranging from strict contact precautions, active surveillance through to stewardship, the training of staff, environment cleaning and coordination at regional levels.

Proper execution of these measures can help bring about significant improvements in patient outcomes and drastically reduce the incidence of CRE infections. Screening and Surveillance both patients and healthcare workers on the presence of carbapenem-resistant Enterobacteriaceae (CRE) is one of the most important components of infection control in reducing the spread of the resistant organisms. Several techniques have been applied to screen and intervene upon CRE-positive patients and workers. Rectal swabs are one of the most basic screening methods which are active surveillance cultures documented to be effective in the identification of CRE asymptomatic carriers. For instance, it is recorded that at the seventh day of stay in the hospital, all patients in the ICU received systematic screening by rectal swabs; this systematically filtered out all the colonized patients (Tiri et al., 2020).This is most especially true in areas such as intensive care units and long-term care settings in which CRE colonization would probably be much more common (Gomides et al., 2022; Tang et al., 2016). Research studies show that screening cultures can identify as high as 52% of cases in some groups while active surveillance has been known to detect a considerable number of individuals with CRE colonization (Kang et

al., 2019). In addition, infection control activation is required. Active includes contact isolation precautions among confirmed carriers, cohousing among patients with CRE, and good hand hygiene by the provider (Richter & Marchaim, 2016). Kotb et al. (2020) CDC and WHO proposed some guidelines that mention some improvement strategies at the point of healthcare. Additionally, implementation of antimicrobial stewardship programs should be incorporated to minimize the inappropriate use of antibiotics that can facilitate the development and dispersal of CRE (Richter & Marchaim, 2016; Kamio & Espinoza, 2022).

More importantly, to effectively screen for and manage CRE, good interfacility communication is required between healthcare facilities. Shimasaki et al. (2018) reported that an important need for interfacility communication to identify patients transferred from LTACHs is necessary due to the presence of a one in three rate of CRE carriage. To prevent CRE, regional cooperations are important, for they can lead to well-coordinated and efficient processes of screening (Lutgring & Limbago, 2016). Antimicrobial Stewardship Programs (ASPs)By optimizing antibiotic usage, ASPs significantly reduce the selective pressure from the development of CRE. The major goal is to reduce needless prescriptions, which is one of the main causes of AMR (Bishop, 2016; Krummenauer, 2023). The wrong or excessive use of antibiotics causes the overgrowth of resistant strains, thus creating the selective pressure in favor of a particular type of microorganism, like CRE. Good stewardship in health care services is very important. The highest goals of ASPs are making antibiotics available only, when necessary, that is, only in specific cases, and use of the right antibiotic. The right drug should therefore also be accompanied by finding out the right dosage to take and the duration of treatment required (Ohl & Ashley, 2011; Pollack & Srinivasan, 2014). Studies have revealed that the overuse of broad-spectrum antibiotics significantly increases the prospects of developing CRE. ASPs are, therefore, likely to reduce the selective pressure that favors resistant organisms, as they encourage the application of narrow-spectrum antibiotics based on appropriateness of use (Krummenauer, 2023; Swaminathan et al., 2013).

**Table 2:** Infection Control Measures for CRE.

| Measure | Description | Examples | References |
|---|---|---|---|
| Contact Precautions | Use of PPE and isolation of infected patients. | Gloves, gowns, and cohorting | (Loon et al., 2018; Epson et al., 2014) |
| Active Surveillance | Routine screening of high-risk patients for asymptomatic colonization. | Rectal swabs in ICU patients | (Ling et al., 2015; Guh et al., 2014) |
| Antimicrobial Stewardship | Optimizing antibiotic use to reduce selective pressure. | Restricting carbapenem use | (Nair & Vaz, 2013; Decraene et al., 2018) |
| Environmental Cleaning | Regular disinfection of high-touch surfaces and equipment. | UV light disinfection, advanced cleaning agents | (Kanamori et al., 2017; Mularoni et al., 2019) |
| Staff Education and Training | Educating healthcare workers on infection prevention protocols. | Hand hygiene training | (Sakai et al., 2021; Park et al., 2023) |

Thirdly, ASPs are aimed at informing medical practitioners on the impact of the antibiotics and resistance. This would be critical since compliance among health-care practitioners toward stewardship recommendations has been found to vary (Duane et al., 2013). ASPs therefore create an environment of appropriate antibiotic usage that leads to a decreased overall antibiotic exposure in a health-care setting and subsequently limits the chance of resistance emerging (Bishop, 2016; Wang et al., 2022). In particular, the IDSA highlights that ASPs work not only to optimize clinical outcomes but also to minimize the unintended consequences of antimicrobial use, including the emergence of resistant pathogens (Bishop, 2016). Aside from improving the prescribing practice of antibiotics, most ASPs often partner with infection prevention programs for general patient safety. In preventing multidrug-resistant organism HAIs, CRE included, their collaboration becomes a more vital mechanism (Assi et al., 2021; Manning et al., 2018). It then connects the strategies for preventing infections and for using antimicrobial agents with one another. Besides, studies further reveal that ASP adoption significantly decreases the occurrence rates of infections resulting from multidrug-resistant microorganisms. For example, meta-analyses have shown that infection-related length of stay can decrease as well as the improvement in clinical outcomes of patients with ASP intervention because of the reduction of resistant pathogen-related infections (Karanika et al., 2016). This underlines the ability of ASPs not only to prevent the development of resistance but also to improve the quality of care rendered to the patient.

## 4. Outbreak Management

Hospitals should respond to the outbreaks regarding carbapenem-resistant Enterobacteriaceae with a thoroughly and variably designed approach that would include methods such as stringent infection protocols, proactive and longitudinal monitoring, collaboration among all medical professionals, and adherence to the principles of antimicrobial stewardship. Strict infection control measures have been one of the strategies adopted in controlling CRE outbreaks. This is by immediate isolation of the infected or colonized patients to reduce further transmission. The practice of cohorting patients and health care workers who take care of the patients to avoid cross-contamination is recommended (Chen et al., 2019; Epson et al., 2014). For example, in the case of an outbreak due to CRE, it has been established that cohorting patients according to screening results is one of the main factors in preventing the spread of infection (Chen et al., 2019).

In addition, contact precautions, such as donning gloves and gowns, are very important in preventing healthcare-associated infections (Decraene et al., 2018). Another vital component of outbreak response is active surveillance. Hospitals need to conduct routine screening for high-risk populations, like ICU patients and those staying in hospitals for a protracted period, for asymptomatic CRE carriers (Pisney et al., 2014; Viale et al., 2015). The implementation of rectal screening has been observed to be effective in identifying carriers during outbreaks; therefore, the intervention can occur at an appropriate time (Pisney et al., 2014).

**Table 3:** Challenges in Managing CRE Outbreaks.

| Challenge | Description | Potential Solutions | References |
|---|---|---|---|
| Resource Limitations | Lack of financial and human resources for surveillance and infection control. | Increased funding and resource allocation | (Bhargava et al., 2014; Gomides et al., 2022) |
| Healthcare Worker Knowledge Gaps | Insufficient training on infection prevention and control. | Regular staff education programs | (Pawłowska et al., 2023) |
| Rapid Evolution of CRE Strains | Emergence of new resistance mechanisms complicates infection control. | Genomic surveillance, real-time analytics | (Chang et al., 2021) |
| Inadequate Antimicrobial Stewardship | Lack of integration with infection control practices. | Collaborative ASPs and infection protocols | (Lee et al., 2023) |

Moreover, there is a need for continued environmental surface and equipment monitoring since CRE can survive even in a well-cleaned hospital environment (Snitkin et al., 2012). Antimicrobial stewardship programs (ASPs) are important in reducing selective pressure that leads to the development of CRE. Optimal antibiotic prescribing practices with minimal use of broad-spectrum antibiotics will prevent the development of resistance (Kwon, 2024; Aiesh et al., 2023). Hospitals should integrate their ASPs with infection control measures to have a culture of responsible use of antibiotics among the healthcare providers (Bishop, 2016). This would be important in ensuring that CRE outbreaks are controlled effectively. Besides, coordination between healthcare professionals requires good communication in response to CRE outbreaks. Good lines of communication can help to hasten the identification and management of cases between infection control teams, microbiology laboratories, and clinical staff (Lee et al., 2013). Sharing information concerning the prevalence of CRE in a region can prepare the hospitals well in advance and prepare relevant control measures as soon as possible (Epson et al., 2014). Last, hospitals should participate in perpetual training and education of healthcare personnel on infection control practices as well as adherence to such protocols during outbreaks. Some aspects include the hand hygiene technique, proper utilization of personal protective equipment (PPE), and reporting any cases suspected of CRE (Liu et al., 2017). Training may be necessary to reinforce the practice on the part of all hospital staff. Therefore, hospitals should respond to CRE outbreaks with a multiple approach of strict infection measures, active surveillance, adding antimicrobial stewardship, providing effective communication, and teaching the health staff on an educational basis. These are strategies to prevent the spread and protect CRE patients.

## 5. Challenges and Barriers

The outbreak and spread of carbapenem-resistant Enterobacteriaceae are a challenge to the health care system; therefore, there is a need to understand the challenges and barriers in managing infections in hospitals. Among the factors said to have contributed to the failure of controlling the CRE outbreaks include lack of resources, poor knowledge of the healthcare providers, and systemic problems of health care facilities. One of the major challenges is having limited

resources for active surveillance and infection control measures. Most settings, particularly those in underdeveloped countries, experience a significant financial and human resource hindrance in implementing efficient screening and monitoring programs for CRE. Bhargava et al. (2014); Gomides et al. (2022). The shortage may contribute to the delayed detection and isolation of infected or colonized patients, allowing CRE to proliferate in healthcare settings. Ling et al., 2015. Further, lack of training and education for the health workers regarding infection control practices often remains a major challenge that aggravates the situation (Pawłowska et al., 2023).

Second, one important area remains the knowledge on infection control by the healthcare practitioners. Even though there is awareness concerning hand hygiene and other preventive practices about infection, most workers suffer from time pressures such that their work is challenged to observe the necessary practice about infection (Pawłowska et al., 2023). Indications show that healthcare employees in other places are neither well-trained nor educated concerning the procedures that should prevent the spread of CRE that could result in infection control breaches (Pawłowska et al., 2023). Specifically, this has been scary within ICU settings, given the often-reported higher occurrence rate of CRE compared with other sites (Tang et al., 2016). Moreover, managing CRE outbreaks is complicated by variability in local epidemiology and the emergence of new resistance mechanisms. This rapid evolution of CRE strains, including novel carbapenemases, complicates the infection control teams in keeping abreast with the best strategies for prevention and management (Chang et al., 2021). This complicates the matter since CRE does not spread only in a healthcare environment but also spreads in communities, therefore needing an extensive surveillance and control system (Pawłowska et al., 2023). Another important action that would be undertaken in dealing with the selective pressure responsible for the spread of CRE is the introduction of ASPs.

However, the support of hospital administration is limited, and ASPs are poorly integrated into infection control practices (Lee et al., 2023; Lee et al., 2023). In that case, the implementation of management of CRE outbreaks as coordinated efforts emphasizing both antimicrobial stewardship and infection prevention will provide a scope for meaningful management of such outbreaks. In summary, challenges to the control of nosocomial CRE outbreaks will be constrained by resource-restricted surveillance and infection-control capacities; lack of available information about healthcare workers involved in infections; the challenging epidemiological scenario of the locus; and inadequate antimicrobial stewardship. A successful strategy against such challenges would hence demand comprehensive and multi-element strategies incorporating more training, resource reinforcement, and convergence of infection prevention and control efforts with antimicrobial stewardship activities.

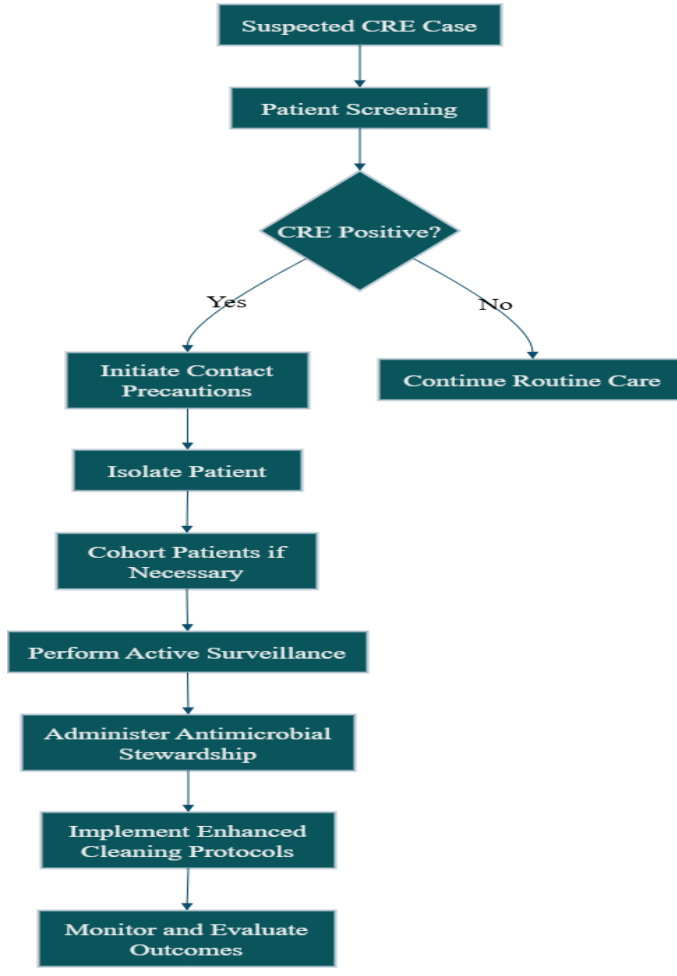


**Figure 1.** This shows the Systematic Approach to Infection Control for Carbapenem-Resistant Enterobacteriaceae (CRE): A structured workflow emphasizing patient screening, isolation, contact precautions, antimicrobial stewardship, active surveillance, and cleaning protocols to mitigate the spread of CRE in healthcare settings.

## 6. Future Directions

Innovations in infection control will be imperative to enhance the management of carbapenem-resistant Enterobacteriaceae in hospitals. With the trend of CRE's prevalence on the rise, healthcare facilities will have to shift to new approaches and technologies that will enhance infection prevention. Innovative approaches for better management of CRE would include

advanced surveillance systems, enhanced environmental cleaning protocols, using probiotics, and integrating the approach of antimicrobial stewardship with the infection control measures. One of the hopeful innovations is the adoption of advanced surveillance systems that entail real-time analytics of the data in monitoring rates of infections and even anticipating outbreaks of CRE. Electronic health records and other techniques of data mining would be applied to allow tracking the admissions of patients, patterns of usage of antibiotics, and infection patterns better (Goedken et al., 2020). In such a way, this preventive strategy may thus enable time to take interventions and control infection measures directed at sources of CRE in the health care setting, which reduces the rate of its transmission (Cai et al., 2022).

Additionally, genomic sequencing offers insights into the dynamics of CRE. It allows health care facilities to identify sources of outbreaks and use containment based on such information (Dong et al., 2020). Better environmental cleaning practices are another infection control innovation. Application of UV light disinfection and advanced cleaners will drastically reduce the bioburden related to CRE on surfaces and in equipment in the healthcare facility (Lee, 2023). Clinical studies have shown that surface UV disinfection can significantly reduce the prevalence of CRE by eliminating the germs on contaminated surfaces, thus preventing transmission to patients and healthcare workers (Mularoni et al., 2019). Besides that, environmental monitoring of the facility daily would ensure proper cleaning protocols and disinfected high-touch surfaces (Park et al., 2023). This is an emerging area of investigation that may be beneficial to infection control: the role of probiotics for the prevention of CRE colonization. Probiotics may help restore the balance in the gut microbiome of a patient, which can lessen the chances of acquiring the CRE, especially in high-risk patient populations such as those confined in intensive care units or ICUs (Lee, 2023).

Maintaining a healthy microbiome, probiotics could be the adjuncts to traditional infection control strategies that enhance overall patient outcomes (Vlad et al., 2022). Integrating ASPs and infection control efforts would be one of the biggest ways to counter the selective pressure that drives the emergence of CRE. ASPs have dedicated efforts toward optimizing the use of antibiotics for the least development of resistance. Infection control measures, on the other hand, are specifically undertaken to avoid the spread of resistant organisms (Loon et al., 2018). Hospitals can, through encouraging teamwork between infection control teams and antimicrobial stewardship programs, offer all-rounded handling of CREs, both in preventing their occurrence and in the process of treatment (Yang et al., 2020).The integration could work to have patients abide by infection control protocols and, consequently, antibiotics more, and fewer infections would be caused by these CREs (Nachamuthu, 2023). Conclusions In brief, innovations in infection control include advanced surveillance systems and enhanced environmental cleaning protocols using probiotics. Incorporating antimicrobial stewardship into a holistic approach with infection control measures is critical to the overall improvement of management for CRE in hospital settings. In so doing, healthcare facilities are able to enhance the ability of preventing and controlling outbreaks within the facility to ensure a safer environment and improved patient care.

Abbreviations

| Abbreviation | Full Form |
|---|---|
| CRE | Carbapenem-Resistant Enterobacteriaceae |

| | |
|---|---|
| KPC | Klebsiella pneumoniae carbapenemase |
| NDM | New Delhi metallo-β-lactamase |
| VIM | Verona integron-encoded metallo-β-lactamase |
| HAI | Healthcare-Associated Infections |
| ICU | Intensive Care Unit |
| PPE | Personal Protective Equipment |
| ASP | Antimicrobial Stewardship Program |
| LTACH | Long-Term Acute Care Hospitals |
| MDRO | Multidrug-Resistant Organisms |

## 8. Conclusions

Carbapenem-resistant Enterobacteriaceae (CRE) poses one of the greatest challenges faced by healthcare systems worldwide owing to their high morbidity and mortality and resistance to last-line antibiotics. The rapid increase in CRE infections necessitates immediate, comprehensive interventions for controlling their spread and impact. Infection control measures include contact precautions, active surveillance, environmental cleaning, and antimicrobial stewardship; therefore, these can also help manage CRE outbreaks. Similarly, the other areas to be addressed would involve resources, knowledge gaps within health care workers, and the fast-evolving mechanism of resistance. Innovations, such as genomic surveillance, real-time analytics, and the integration of probiotics, will form a basis for developing new infection prevention strategies. Proper management of CRE needs international cooperation, continued research, and coordinating infection control practices with antimicrobial stewardship for better patient outcomes and a safer health care environment.

Conflict of Interest

The authors affirm that they have no financial, personal or other conflicts of interest.

Author contributions

The final paper was examined and authorized for submission by all authors, who also committed to taking responsibility for every part of the work to guarantee accuracy and integrity. The first author provides the idea and writes the initial draft of the text. The corresponding author oversees the entire work, makes significant critical edits, and gives the final draft approval for submission.

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## WORKS CITED

Abouelfetouh, A., Torky, A., & Aboulmagd, E. (2019). Phenotypic and genotypic characterization of carbapenem-resistant acinetobacter baumannii isolates from egypt. Antimicrobial Resistance and Infection Control, 8(1). https://doi.org/10.1186/s13756-019-0611-6

Kamio, K. and Espinoza, J. (2022). The predominance of klebsiella aerogenes among carbapenem-resistant enterobacteriaceae infections in japan. Pathogens, 11(7), 722. https://doi.org/10.3390/pathogens11070722

Swaminathan, M., Sharma, S., Blash, S., Patel, G., Banach, D., Phillips, M., … & Calfee, D. (2013). Prevalence and risk factors for acquisition of carbapenem-resistant enterobacteriaceae in the setting of endemicity. Infection Control and Hospital Epidemiology, 34(8), 809-817. https://doi.org/10.1086/671270

Ojo, A., Adebajo, S., Fasina, k., Odejinmi, B., Ojo, O., Ooladotun, a., … & Ibeaha, J. (2020). Phenotypic detection of carbapenem resistant enterobacteriaceae and characterization of klebsiella pneumoniae carbapenemase(kpc) producing klebsiella pneumonia. Microbes and Infectious Diseases, 0(0), 0-0. https://doi.org/10.21608/mid.2020.36999.1040

Dong, L., Espinoza, H., & Espinoza, J. (2020). Emerging superbugs: the threat of carbapenem resistant enterobacteriaceae. Aims Microbiology, 7(3), 176-182. https://doi.org/10.3934/microbiol.2020012

Okello, W. (2023). Detection of carbapenem resistance genes incampylobacter coliandcampylobacter jejuniisolated from chickens, and diarrheic children aged less than five years in kampala city, uganda. https://doi.org/10.1101/2023.09.10.23295341

Zaman, T., Alrodayyan, M., Albladi, M., Aldrees, M., Siddique, M., Aljohani, S., … & Balkhy, H. (2018). Clonal diversity and genetic profiling of antibiotic resistance among multidrug/carbapenem-resistant klebsiella pneumoniae isolates from a tertiary care hospital in saudi arabia. BMC Infectious Diseases, 18(1). https://doi.org/10.1186/s12879-018-3114-9

Rajni, E., Rajpurohit, V., Rathore, P., & Khatri, P. (2018). Epidemiology of carbapenem-resistant enterobacteriaceae colonization in icu: a pilot study from a tertiary care hospital in western rajasthan, india. International Journal of Research in Medical Sciences, 6(10), 3340. https://doi.org/10.18203/2320-6012.ijrms20184043

Brennan, B., Coyle, J., Marchaim, D., Pogue, J., Boehme, M., Finks, J., … & Kaye, K. (2014). Statewide surveillance of carbapenem-resistant enterobacteriaceae in michigan. Infection Control and Hospital Epidemiology, 35(4), 342-349. https://doi.org/10.1086/675611

Nachamuthu, S. (2023). Carbapenem-resistant enterobacteriaceae bacteraemia in intensive care unit: a descriptive study on risk factors and clinical outcome. Iium Medical Journal Malaysia, 22(4). https://doi.org/10.31436/imjm.v22i4.2272

Siddica, A., Hasan, B., Alam, S., Nahar, S., Begum, N., & Aftab, S. (2020). Pattern of carbapenem resistance in enterobacteriaceae in rajshahi medical college hospital. Taj Journal of Teachers Association, 33(2), 63-68. https://doi.org/10.3329/taj.v33i2.51341

Karanika, S., Paudel, S., Grigoras, C., Kalbasi, A., & Mylonakis, E. (2016). Systematic review and meta-analysis of clinical and economic outcomes from the implementation of hospital-based antimicrobial stewardship programs. Antimicrobial Agents and Chemotherapy, 60(8), 4840-4852.

Aiesh, B., Nazzal, M., Abdelhaq, A., Abutaha, S., Zyoud, S., & Sabateen, A. (2023). Impact of an antibiotic stewardship program on antibiotic utilization, bacterial susceptibilities, and cost of antibiotics. Scientific Reports, 13(1). https://doi.org/10.1038/s41598-023-32329-6

Musa, A. (2023). Detection of carbapenem resistance among enterobacteriaceae pathogens isolated from clinical samples in shendi locality. Middle East Research Journal Microbiology and Biotechnology, 3(02), 43-47. https://doi.org/10.36348/merjmb.2023.v03i02.004

Bishop, B. (2016). Antimicrobial stewardship in the emergency department. Journal of Pharmacy Practice, 29(6), 556-563. https://doi.org/10.1177/0897190015585762

Premanadham, N., Munilaxmi, S., & Kumar, A. (2022). Prevalence of carbapenem resistant enterobacteriaceae isolated in tertiary care hospital in nmc and hospital, nellore, andhra pradesh, india.

International Journal of Current Microbiology and Applied Sciences, 11(4), 122-127. https://doi.org/10.20546/ijcmas.2022.1104.017

Shi, M. (2021). "overview of carbapenem-resistant enterobacteriaceae". Biomedical Journal of Scientific & Technical Research, 39(2). https://doi.org/10.26717/bjstr.2021.39.006285

Richter, S. and Marchaim, D. (2016). Screening for carbapenem-resistant enterobacteriaceae: who, when, and how?. Virulence, 8(4), 417-426. https://doi.org/10.1080/21505594.2016.1255381

Peng, Z., Li, X., Hu, Z., Li, Z., Lv, Y., Lei, M., … & Wang, X. (2019). Characteristics of carbapenem-resistant and colistin-resistant escherichia coli co-producing ndm-1 and mcr-1 from pig farms in china. Microorganisms, 7(11), 482. https://doi.org/10.3390/microorganisms7110482

Abe, R., Hagiya, H., Akeda, Y., Yamamoto, N., Ishii, Y., & Tomono, K. (2019). Bactericidal efficacy of meropenem in combination with cefmetazole against imp-producing carbapenem-resistant enterobacteriaceae.. https://doi.org/10.21203/rs.2.15806/v3

Cai, Y., Hoo, G., Lee, W., Tan, B., Yoong, J., Teo, Y., … & Kwa, A. (2022). Estimating the economic cost of carbapenem resistant enterobacterales healthcare associated infections in singapore acute-care hospitals. Plos Global Public Health, 2(12), e0001311. https://doi.org/10.1371/journal.pgph.0001311

Majlander, J., Anttila, V., Nurmi, W., Seppälä, A., Tiedje, J., & Muziasari, W. (2021). Routine wastewater-based monitoring of antibiotic resistance in two finnish hospitals: focus on carbapenem resistance genes and genes associated with bacteria causing hospital-acquired infections. Journal of Hospital Infection, 117, 157-164. https://doi.org/10.1016/j.jhin.2021.09.008

Yang, T., Luo, X., Yang, Q., Chen, H., Luo, Y., Zhao, Y., … & Shi, J. (2020). Different screening frequencies of carbapenem-resistant enterobacteriaceae in patients undergoing hematopoietic stem cell transplantation: which one is better?. Antimicrobial Resistance and Infection Control, 9(1). https://doi.org/10.1186/s13756-020-0706-0

Lai, C., Chen, C., Lu, Y., Chuang, Y., & Tang, H. (2018). In vitro activity of cefoperazone and cefoperazone-sulbactam against carbapenem-resistant <em>acinetobacter baumannii</em> and <em>pseudomonas aeruginosa</em>. Infection and Drug Resistance, Volume 12, 25-29. https://doi.org/10.2147/idr.s181201

Dogonchi, A., Ghaemi, E., Ardebili, A., Yazdansetad, S., & Pournajaf, A. (2018). Metallo-β-lactamase-mediated resistance among clinical carbapenem-resistant pseudomonas aeruginosa isolates in northern iran: a potential threat to clinical therapeutics. Tzu Chi Medical Journal, 30(2), 90. https://doi.org/10.4103/tcmj.tcmj_101_17

Chang, E., Chang, H., Shin, I., Oh, Y., Kang, C., Choe, P., … & Kim, N. (2021). Investigation of transmission rate of carbapenemase-producing carbapenem-resistant enterobacteriaceae among contacted patients and healthcare workers in a tertiary hospital.. https://doi.org/10.21203/rs.3.rs-461648/v1

Lee, T., Cho, M., Lee, J., Hwang, J., Lee, C., & Chung, K. (2021). Molecular characterization of carbapenem-resistant, colistin-resistant klebsiella pneumoniae isolates from a tertiary hospital in jeonbuk, korea. Journal of Bacteriology and Virology, 51(3), 120-127. https://doi.org/10.4167/jbv.2021.51.3.120

Park, Y., Son, E., Choe, Y., Kang, C., Roh, S., Hwang, Y., … & Bang, J. (2023). Outbreak of carbapenem-resistant enterobacterales at a long-term care facility in seoul, korea: surveillance and intervention mitigation strategies. Epidemiology and Health, 45, e2023057. https://doi.org/10.4178/epih.e2023057

Goedken, C., Guihan, M., Brown, C., Ramanathan, S., Vivo, A., Suda, K., … & Evans, C. (2020). Evaluation of carbapenem-resistant enterobacteriaceae (cre) guideline implementation in the veteran's affairs medical centers using the consolidated framework for implementation research.. https://doi.org/10.21203/rs.3.rs-54590/v1

Haytoğlu, Z., Gündeşlioğlu, Ö., Yıldızdaş, D., Kocabaş, E., Alabaz, D., & Horoz, Ö. (2020). Carbapenem and colistin resistance in children with enterobacteriaceae infections. The Turkish Journal of Pediatrics, 62(5), 778-786. https://doi.org/10.24953/turkjped.2020.05.009

Marusinec, R. (2024). Epidemiology of carbapenem-resistant organisms in alameda county, california, 2019–2021. Antimicrobial Stewardship & Healthcare Epidemiology, 4(1). https://doi.org/10.1017/ash.2024.33

Conlan, S., Thomas, P., Deming, C., Park, M., Lau, A., Dekker, J., … & Segre, J. (2014). Single-molecule sequencing to track plasmid diversity of hospital-associated carbapenemase-producing enterobacteriaceae. Science Translational Medicine, 6(254). https://doi.org/10.1126/scitranslmed.3009845

Patel, G. and Bonomo, R. (2013). “stormy waters ahead”: global emergence of carbapenemases. Frontiers in Microbiology, 4. https://doi.org/10.3389/fmicb.2013.00048

Pawłowska, I., Ziółkowski, G., Jachowicz-Matczak, E., Stasiowski, M., Gajda, M., & Wójkowska-Mach, J. (2023). Colonization and healthcare-associated infection of carbapenem-resistant enterobacteriaceae, data from polish hospital with high incidence of carbapenem-resistant enterobacteriaceae, does active target screening matter?. Microorganisms, 11(2), 437. https://doi.org/10.3390/microorganisms11020437

Kang, J., Yi, J., Ko, M., Lee, S., Lee, J., & Kim, K. (2019). Prevalence and risk factors of carbapenem-resistantenterobacteriaceaeacquisition in an emergency intensive care unit in a tertiary hospital in korea: a case-control study. Journal of Korean Medical Science, 34(18). https://doi.org/10.3346/jkms.2019.34.e140

Assi, M., Abbas, S., Nori, P., Doll, M., Godbout, E., Bearman, G., … & Stevens, M. (2021). Infection prevention and antimicrobial stewardship program collaboration during the covid-19 pandemic: a window of opportunity. Current Infectious Disease Reports, 23(10). https://doi.org/10.1007/s11908-021-00759-w

Decraene, V., Phan, H., George, R., Wyllie, D., Akinremi, O., Aiken, Z., … & Cawthorne, J. (2018). A large, refractory nosocomial outbreak of klebsiella pneumoniae carbapenemase-producing escherichia coli demonstrates carbapenemase gene outbreaks involving sink sites require novel approaches to infection control. Antimicrobial Agents and Chemotherapy, 62(12). https://doi.org/10.1128/aac.01689-18

Dinkarrao, N. (2023). Detecting carbapenem resistance in enterobacteriaceae isolates using carbapenem discs and the modified hodge test at a tertiary care hospital in maharashtra, india. JoMMID, 11(4), 185-191. https://doi.org/10.61186/jommid.11.4.185

Krummenauer, E. (2023). A nationwide survey of antimicrobial stewardship in pediatric intensive care unit: implementation notes from the brazilian underground. Antimicrobial Stewardship & Healthcare Epidemiology, 3(1). https://doi.org/10.1017/ash.2023.530

Manning, M., Septimus, E., Ashley, E., Cosgrove, S., Fakih, M., Schweon, S., … & Moody, J. (2018). Antimicrobial stewardship and infection prevention—leveraging the synergy: a position paper update. Infection Control and Hospital Epidemiology, 39(4), 467-472. https://doi.org/10.1017/ice.2018.33

Ohl, C. and Ashley, E. (2011). Antimicrobial stewardship programs in community hospitals: the evidence base and case studies. Clinical Infectious Diseases, 53(suppl_1), S23-S28. https://doi.org/10.1093/cid/cir365

Martin, A., Fahrbach, K., Zhao, Q., & Lodise, T. (2018). Association between carbapenem resistance and mortality among adult, hospitalized patients with serious infections due to enterobacteriaceae: results of a systematic literature review and meta-analysis. Open Forum Infectious Diseases, 5(7). https://doi.org/10.1093/ofid/ofy150

Lee, J. (2023). Role of probiotics in preventing carbapenem-resistant enterobacteriaceae colonization in the intensive care unit: risk factors and microbiome analysis study. Microorganisms, 11(12), 2970. https://doi.org/10.3390/microorganisms11122970

Pisney, L., Barron, M., Kassner, E., Havens, D., & Madinger, N. (2014). Carbapenem-resistant enterobacteriaceae rectal screening during an outbreak of new delhi metallo-β-lactamase–producing klebsiella pneumoniae at an acute care hospital. Infection Control and Hospital Epidemiology, 35(4), 434-436. https://doi.org/10.1086/675597

Chen, W., Yong, Y., & Tan, B. (2019). Increased mortality among carbapenemase-producing carbapenem-resistant enterobacteriaceae carriers who developed clinical isolates of another genotype. Open Forum Infectious Diseases, 6(2). https://doi.org/10.1093/ofid/ofz006

Nair, P. and Vaz, M. (2013). Prevalence of carbapenem resistant enterobacteriaceae from a tertiary care hospital in mumbai, india. Journal of Microbiology and Infectious Diseases, 03(04), 207-210. https://doi.org/10.5799/ahinjs.02.2013.04.0110

Liu, J., Yu, J., Chen, F., Yu, J., Simner, P., Liu, Y., … & Shen, L. (2017). Emergence and establishment of kpc-2-producing st11 klebsiella pneumoniae in a general hospital in shanghai, china. European Journal of Clinical Microbiology & Infectious Diseases, 37(2), 293-299. https://doi.org/10.1007/s10096-017-3131-4

Guh, A., Limbago, B., & Kallen, A. (2014). Epidemiology and prevention of carbapenem-resistant enterobacteriaceae in the united states. Expert Review of Anti-Infective Therapy, 12(5), 565-580. https://doi.org/10.1586/14787210.2014.902306

Lee, S., Kim, C., Lee, H., Park, K., & Han, S. (2023). Epidemiology of carbapenem-resistant <em>enterobacteriaceae </em>bacteremia in the gyeonggi province, republic of korea, between 2018 and 2021.. https://doi.org/10.20944/preprints202306.2188.v1

Mularoni, A., Douradinha, B., Campanella, O., Hazen, B., Medaglia, A., Arena, G., … & Gridelli, B. (2019). Epidemiology and successful containment of a carbapenem-resistant enterobacteriaceae outbreak in a southern italian transplant institute. Transplant Infectious Disease, 21(4). https://doi.org/10.1111/tid.13119

Lee, G., Lawson, K., & Burgess, D. (2013). Clinical epidemiology of carbapenem-resistant enterobacteriaceae in community hospitals. Annals of Pharmacotherapy, 47(9), 1115-1121. https://doi.org/10.1177/1060028013503120

Ghafur, A., Nagvekar, V., Thilakavathy, S., Chandra, K., Gopalakrishnan, R., & Vidyalakshmi, P. (2012). “save antibiotics, save lives”: an indian success story of infection control through persuasive diplomacy. Antimicrobial Resistance and Infection Control, 1(1), 29. https://doi.org/10.1186/2047-2994-1-29

Viale, P., Tumietto, F., Giannella, M., Bartoletti, M., Tedeschi, S., Ambretti, S., … & Lewis, R. (2015). Impact of a hospital-wide multifaceted programme for reducing carbapenem-resistant enterobacteriaceae infections in a large teaching hospital in northern italy. Clinical Microbiology and Infection, 21(3), 242-247. https://doi.org/10.1016/j.cmi.2014.10.020

Loon, K., holt, A., & Vos, M. (2018). A systematic review and meta-analyses of the clinical epidemiology of carbapenem-resistant enterobacteriaceae. Antimicrobial Agents and Chemotherapy, 62(1). https://doi.org/10.1128/aac.01730-17

Tiri, B., Sensi, E., Marsiliani, V., Cantarini, M., Priante, G., Vernelli, C., … & Cappanera, S. (2020). Antimicrobial stewardship program, covid-19, and infection control: spread of carbapenem-resistant klebsiella pneumoniae colonization in icu covid-19 patients. what did not work?. Journal of Clinical Medicine, 9(9), 2744. https://doi.org/10.3390/jcm9092744

Tang, H., Hsieh, C., Chang, P., Chen, J., Lin, Y., Lai, C., … & Chuang, Y. (2016). Clinical significance of community- and healthcare-acquired carbapenem-resistant enterobacteriaceae isolates. Plos One, 11(3), e0151897. https://doi.org/10.1371/journal.pone.0151897

Ling, M., Tee, Y., Tan, S., Amin, I., How, K., Tan, K., … & Lee, L. (2015). Risk factors for acquisition of carbapenem resistant enterobacteriaceae in an acute tertiary care hospital in singapore. Antimicrobial Resistance and Infection Control, 4(1). https://doi.org/10.1186/s13756-015-0066-3

Vlad, N., Cernat, R., Carp, S., Mitan, R., Dumitru, A., Nemet, C., … & Dumitru, I. (2022). Predictors of carbapenem-resistant enterobacteriaceae (cre) strains in patients with covid-19 in the icu ward: a retrospective case–control study. Journal of International Medical Research, 50(10). https://doi.org/10.1177/03000605221129154

Yoshida, I., Takata, I., Fujita, K., Takashima, H., & Sugiyama, H. (2022). Tp0586532, a novel non-hydroxamate lpxc inhibitor: potentiating effect on in vitro activity of meropenem against carbapenem-resistant enterobacteriaceae. Microbiology Spectrum, 10(3). https://doi.org/10.1128/spectrum.00828-22

Sakai, Y., Gotoh, K., Nakano, R., Iwahashi, J., Miura, M., Horita, R., … & Watanabe, H. (2021). Infection control for a carbapenem-resistant enterobacteriaceae outbreak in an advanced emergency medical services center. Antibiotics, 10(12), 1537. https://doi.org/10.3390/antibiotics10121537

Duane, T., Zuo, J., Wolfe, L., Bearman, G., Edmond, M., Lee, K., … & Stevens, M. (2013). Surgeons do not listen: evaluation of compliance with antimicrobial stewardship program recommendations. The American Surgeon, 79(12), 1269-1272. https://doi.org/10.1177/000313481307901218

Wang, Y., Zhou, C., Liu, C., Liu, S., Liu, X., & Li, X. (2022). The impact of pharmacist-led antimicrobial stewardship program on antibiotic use in a county-level tertiary general hospital in china: a retrospective study using difference-in-differences design. Frontiers in Public Health, 10. https://doi.org/10.3389/fpubh.2022.1012690

Sheu, C., Chang, Y., Lin, S., Chen, Y., & Hsueh, P. (2019). Infections caused by carbapenem-resistant enterobacteriaceae: an update on therapeutic options. Frontiers in Microbiology, 10. https://doi.org/10.3389/fmicb.2019.00080

Schechner, V., Kotlovsky, T., Tarabeia, J., Kazma, M., Schwartz, D., Navon-Venezia, S., … & Carmeli, Y. (2011). Predictors of rectal carriage of carbapenem-resistant enterobacteriaceae (cre) among patients with known cre carriage at their next hospital encounter. Infection Control and Hospital Epidemiology, 32(5), 497-503. https://doi.org/10.1086/659762

Zequinão, T., Telles, J., & Gasparetto, J. (2020). Carbapenem stewardship with ertapenem and antimicrobial resistance-a scoping review. Revista Da Sociedade Brasileira De Medicina Tropical, 53. https://doi.org/10.1590/0037-8682-0413-2020

Snitkin, E., Zelazny, A., Thomas, P., Stock, F., Henderson, D., Palmore, T., … & Segre, J. (2012). Tracking a hospital outbreak of carbapenem-resistant klebsiella pneumoniae with whole-genome sequencing. Science Translational Medicine, 4(148). https://doi.org/10.1126/scitranslmed.3004129

Thaden, J., Pogue, J., & Kaye, K. (2016). Role of newer and re-emerging older agents in the treatment of infections caused by carbapenem-resistant enterobacteriaceae. Virulence, 8(4), 403-416. https://doi.org/10.1080/21505594.2016.1207834

Yamada, Y. and Suwabe, A. (2013). Diverse carbapenem-resistance mechanisms in 16s rrna methylase-producing acinetobacter baumannii. Journal of Medical Microbiology, 62(4), 618-622. https://doi.org/10.1099/jmm.0.048991-0

Curcio, D. (2013). Antibiotic prescriptions in critically-ill patients: a latin american experience. Annals of Medical and Health Sciences Research, 3(2), 220. https://doi.org/10.4103/2141-9248.113666

Manyahi, J., Moyo, S., Kibwana, U., Goodman, R., Allman, E., Hubbard, A., … & Roberts, A. (2022). First identification of bla ndm-5 producing escherichia coli from neonates and a hiv infected adult in tanzania. Journal of Medical Microbiology, 71(2). https://doi.org/10.1099/jmm.0.001513

Adesanya, O. and Igwe, H. (2020). Carbapenem-resistant <em>enterobacteriaceae</em> (cre) and gram-negative bacterial infections in south-west nigeria: a retrospective epidemiological surveillance study. Aims Public Health, 7(4), 804-815. https://doi.org/10.3934/publichealth.2020062

Epson, E., Pisney, L., Wendt, J., MacCannell, D., Janelle, S., Kitchel, B., … & Bamberg, W. (2014). Carbapenem-resistant klebsiella pneumoniae producing new delhi metallo-β-lactamase at an acute care hospital, colorado, 2012. Infection Control and Hospital Epidemiology, 35(4), 390-397. https://doi.org/10.1086/675607

(2019). Untitled. International Journal of Applied Microbiology and Biotechnology Research, 7(6). https://doi.org/10.33500/ijambr.2019.07.011

Carrilho, C., Oliveira, L., Gaudereto, J., Perozin, J., Urbano, M., Camargo, C., … & Costa, S. (2016). A prospective study of treatment of carbapenem-resistant enterobacteriaceae infections and risk factors associated with outcome. BMC Infectious Diseases, 16(1). https://doi.org/10.1186/s12879-016-1979-z

Gong, X., Zhang, J., Su, S., Fu, Y., Bao, M., Wang, Y., … & Zhang, X. (2018). Molecular characterization and epidemiology of carbapenem non-susceptible enterobacteriaceae isolated from the eastern region of heilongjiang province, china. BMC Infectious Diseases, 18(1). https://doi.org/10.1186/s12879-018-3294-3

Shimasaki, T., Segreti, J., Tomich, A., Kim, J., Hayden, M., Lin, M., … & Program, C. (2018). Active screening and interfacility communication of carbapenem-resistant enterobacteriaceae (cre) in a tertiary-care hospital. Infection Control and Hospital Epidemiology, 39(9), 1058-1062. https://doi.org/10.1017/ice.2018.150

Gomides, M., Fontes, A., Silveira, A., Matoso, D., Luiz-Ferreira, Â., & Sadoyama, G. (2022). The importance of active surveillance of carbapenem-resistant enterobacterales (cre) in colonization rates in critically ill patients. Plos One, 17(1), e0262554. https://doi.org/10.1371/journal.pone.0262554

Lutgring, J. and Limbago, B. (2016). The problem of carbapenemase-producing-carbapenem-resistant-enterobacteriaceae detection. Journal of Clinical Microbiology, 54(3), 529-534. https://doi.org/10.1128/jcm.02771-15

Shanmugam, P., Meenakshisundaram, J., & Jayaraman, P. (2013). Bla kpc gene detection in clinical isolates of carbapenem resistant enterobacteriaceae in a tertiary care hospital. Journal of Clinical and Diagnostic Research. https://doi.org/10.7860/jcdr/2013/7759.3747

Rizzo, K., Horwich-Scholefield, S., & Epson, E. (2019). Carbapenem and cephalosporin resistance among enterobacteriaceae in healthcare-associated infections, california, usa1. Emerging Infectious Diseases, 25(7), 1389-1393. https://doi.org/10.3201/eid2507.181938

Wangchinda, W., Thamlikitkul, V., Watcharasuwanseree, S., & Tangkoskul, T. (2022). Active surveillance for carbapenem-resistant enterobacterales (cre) colonization and clinical course of cre colonization among hospitalized patients at a university hospital in thailand. Antibiotics, 11(10), 1401. https://doi.org/10.3390/antibiotics11101401

Kanamori, H., Parobek, C., Juliano, J., Duin, D., Cairns, B., Weber, D., … & Rutala, W. (2017). A prolonged outbreak of kpc-3-producing enterobacter cloacae and klebsiella pneumoniae driven by multiple mechanisms of resistance transmission at a large academic burn center. Antimicrobial Agents and Chemotherapy, 61(2). https://doi.org/10.1128/aac.01516-16

Pollack, L. and Srinivasan, A. (2014). Core elements of hospital antibiotic stewardship programs from the centers for disease control and prevention. Clinical Infectious Diseases, 59(suppl_3), S97-S100. https://doi.org/10.1093/cid/ciu542

El-Mahdy, R. and El-Kannishy, G. (2019). <p>virulence factors of carbapenem-resistant <em>pseudomonas aeruginosa</em> in hospital-acquired infections in mansoura, egypt</p>. Infection and Drug Resistance, Volume 12, 3455-3461. https://doi.org/10.2147/idr.s222329

Abdalhamid, B., Elhadi, N., Alabdulqader, N., Alsamman, K., & Aljindan, R. (2016). Rates of gastrointestinal tract colonization of carbapenem-resistant enterobacteriaceae and pseudomonas aeruginosa in hospitals in saudi arabia. New Microbes and New Infections, 10, 77-83. https://doi.org/10.1016/j.nmni.2016.01.014

Gohil, S., Singh, R., Chang, J., Gombosev, A., Tjoa, T., Zahn, M., … & Huang, S. (2017). Emergence of carbapenem-resistant enterobacteriaceae in orange county, california, and support for early regional strategies to limit spread. American Journal of Infection Control, 45(11), 1177-1182. https://doi.org/10.1016/j.ajic.2017.06.004

Suwantarat, N. and Carroll, K. (2016). Epidemiology and molecular characterization of multidrug-resistant gram-negative bacteria in southeast asia. Antimicrobial Resistance and Infection Control, 5(1). https://doi.org/10.1186/s13756-016-0115-6

Bhargava, A., Hayakawa, K., Silverman, E., Haider, S., Alluri, K., Datla, S., … & Kaye, K. (2014). Risk factors for colonization due to carbapenem-resistant enterobacteriaceae among patients: exposed to long-term acute care and acute care facilities. Infection Control and Hospital Epidemiology, 35(4), 398-405. https://doi.org/10.1086/675614

Lovison, O., Rau, R., Lima-Morales, D., Almeida, E., Crispim, M., Barreto, F., … & Martins, A. (2020). High-performance method to detection of klebsiella pneumoniae carbapenemase in enterobacterales by lc-ms/ms. Brazilian Journal of Microbiology, 51(3), 1029-1035. https://doi.org/10.1007/s42770-019-00222-y

Kotb, S., Lyman, M., Ismail, G., Fattah, M., Girgis, S., Etman, A., … & Talaat, M. (2020). Epidemiology of carbapenem-resistant enterobacteriaceae in egyptian intensive care units using national healthcare–associated infections surveillance data, 2011–2017. Antimicrobial Resistance and Infection Control, 9(1). https://doi.org/10.1186/s13756-019-0639-7

Kwon, K. (2024). Antimicrobial use and carbapenem-resistant enterobacterales in korea: a nationwide case-control study with propensity score matching. Journal of Korean Medical Science, 39(14). https://doi.org/10.3346/jkms.2024.39.e132