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Carbepenem and carbepenem resistance: an overview.

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Abstract

Antibiotic resistance is a global menace, as the percentage of resistance globally is increasing day by day. The decrease in developing new antimicrobial substances and increase in irrational use of antibiotics supported the emergence of antibiotic resistance. Carbepenem is said to be the priority antibiotic for the treatment of infections caused by gram-negative bacteria. But due to the excessive use, irrational use of this antibiotic and unhygienic environment of hospitals results in the dissemination of carbepenem resistance. Our study reviewed on the resistance mechanisms, reasons of the resiatnce development and global prevalence of carbepenem resiatance.

Keywords: Carbepenem-resistance; Enterobacteriace; Antibiotic resistance; Drug resistance.

Introduction

1. Overview on Carbapenem Resistance

Over the year's resistance against these antibiotics emerged at very high rate causing a major health concern globally (Francis S. Codjoe, et al., 2017). Carbapenem resistance is caused by two mechanisms including the carbapenemases (carbapenem-hydrolyzing enzymes) production and B-lactamase activity along with mutations in its structure (ESBLs & AmpC cephalosporinases) (Teiji Sawa, et al., 2020). Resistance developed in Carbapenem is mainly by acquired or intrinsic resistance mechanisms or by both mechanism, as it is known that bacteria is capable of acquiring many resistance mechanisms which includes mutations in the target site, enzymatic inactivation and efflux pumps. Out of these, enzymatic inactivation mechanism is most well-established (Bilal Aslam, et al., 2020).

Acquired carbapenem resistance mechanisms involves: Carbapenems destruction- carbapenems which are resistant to hydrolysis caused by plasmid AmpCs in coexistence with ESBL enzymes are destructed, lending insusceptibility towards carbapenem agent (Francis S. Codjoe, et al., 2017), Porin mutation including expression modulation Transfer of extended spectrum beta-lactamases genes (ESBL genes) within the organisms (Branka Bedenić, et al., 2014). Intrinsic mechanism of carbapenem resistance encompasses reduction in absorption caused by altered porin channels and also reduction in outer membrane permeability of B-lactam drugs (Georgios Meletis, 2016).

Drivers of carbapenem resistance**:** Some of them results due to prolonged use of drugs like imipenem in hospital settings, prolonged hospital stays (Bilal Aslam, et al., 2020). It has been described that carbapenem resistance among Enterobacteriaceae is promoted when metronidazole destroys the normal flora and translocation frequency is increased (Min-Hyok Jeon, et al., 2008). It is also seen that the rate of carbapenem resistance increases, as soon as the enzymes gene is linked to acquired genetic elements for example with integrons and plasmids (Michael N Alekshun, et al., 2007). Transfer of carbapenem resistant gene in various strains isolated from places like health care facilities are becoming the potential drivers for continuous spread of carbapenem resistance when combined with gene transfer by bacteriophage carrying B-lactamases gene (Maite Muniesa et al., 2004).

2. Carbapenem-resistant Enterobacteriaceae: a major health concern

It is now well known that Enterobacteriaceae is responsible for causing major healthcare-related infections worldwide (Yanling Xu, et al., 2015). More than half of healthcare-related infections are due to Antimicrobial-Resistant Pathogens like Enterobacteriaceae as per the CDC reports. Its spread and the emergence is now a global concern (Lindsey M Weiner et al., 2016). Regulatory authority CDC defines CRE as "Enterobacteriaceae that seems to be tested as resistant to any carbapenem agent including ertapenem or may demonstrate as carbapenemase production through molecular or phenotypic assay". *(*Joseph D Lutgring, *et al, 2016)* There are organisms nearly resistant to therapeutics available today due to the high rate of occurrence of carbapenem resistance in (CRE) including add on resistance genes to a variety of antimicrobial classes. (Latania K Logan, et al., 2012) Carbapenem-resistant Enterobacteriaceae are very difficult to treat and causes high rate of mortality

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(Mehreen Arshad, et al., 2021) E. coli and Klebsiella species can easily become carbapenem resistant. CRE infections commonly occur in healthcare and hospital settings, while the patients on-going prolonged antibiotic treatment are also highly susceptible to these CRE infections (A. P. Magiorakos, et al., 2017).

Epidemiological data on (CP-CRE) varies in different part of world (Latania K. Logan,et al., 2017) An important carbapenemase-producing carbapenem resistance (KPC) was the first identified carbapenemase in the USA in 1996, and the prevalence is distributed unevenly among the US states (Ryan S. Arnold, et al., 2012). Epidemiology of CRE show large spectrum in different region, KPC is an endemic in Israel, whereas VIM in India and NDM in Greece and OXA-48 in Turkey, they all are disseminated successfully around the globe (R Cantón, et al., 2012). So the resolute detection of CP-CRE could be the insipient step to combat such a mounting health concern (Joseph D Lutgring, et al., 2016)

Overall carbapenem resistance in Enterobacteriaceae in Asia

The rise in Colistin resistance is resulting in wide spectra of untreatable infections but due to limited study and non-availability of data there is less awareness, including Southeast Asia (Marissa D.Malchione, et al., 2019) In countries like India, Pakistan, and Vietnam, carbapenem-resistant Enterobacteriaceae is spreading due to bad hygiene and lack of sanitation (Li-Yang Hsu, et al., 2016), The New Delhi metallo-β-lactamase-1 (NDM-1) gene is prevalent in South Asia and is one of the most widely distributed carbapenemases in terms of geographic spread and bacterial species (Karthikeyan K Kumarasamy, et al., 2010). In Asia-Pacific countries like China many plasmids mediated CRE outbreaks were recorded found in CRE clinical isolates (Yi-Wei Tang, et al., 2019)

3. Spectrum of resistance granted by carbapenemases

Carbapenemases consist of three major groups that belong to separate molecular classes (Ambler Rp et al., 1980) KPC belongs to class A, NDM to class B and OXA-48 to class D (Alina Iovleva, et al 2017).

KPC consist of wide range of substrates including penicillins, cephalosporins, classic β-lactamase inhibitors (clavulanic acid, sulbactam and tazobactam), aztreonam and carbapenems thus consist of large spectrum (Timothy Palzkill 2018). Its activity is inhibited by clavulanic acid to some extent but is inhibited well by boronic acid compounds. MBLs including NDM are metalloenzymes that possess zinc in the active site (Francesca Spyrakis,et al., 2020). The spectrum of hydrolysis is similar to that of KPC. Therefore, resistance to carbapenems and susceptibility to aztreonam is suggestive of MBL production; however, it mostly shows co-production of ESBL common in clinical strains, which make them also resistant to aztreonam (Xing Tan, et al., 2021). OXA-48 is a serine β-lactamase like KPC, but has its own unique spectrum of activity which includes penicillins and carbapenems but spares cephalosporins and aztreonam (Branka Bedenić, et al., 2018) However, it is seen that its activity against carbapenems is not as strong as that of KPC and MBLs. That's why, based on susceptibility phenotype, detection of OXA-48-producing Enterobacteriaceae is more exigent to precise irregularitie (Nahed Ismail, et al., 2017).

4. Carbapenem-resistance determinants

It's been known that clinically important bacteria's commonly do not show intrinsic resistance in carbapenem (Georgios Meletis, 2016) whereas mutation is very common in clinically important bacteria. It is seen that some species decrease the permeability of the outer membrane to restrict carbapenems enter their PBPs (Robert A Bonomo, et al., 2006) Gram-positive bacteria through mutational obtained changes become resistant to carbapenems and other beta-lactams of their PBPs. The most important determinants act as barrier of serine β-lactamases by carbapenems are the hydroxyethyl side chain found in every carbapenems and pyrroline ring (Krisztina M. Papp-Wallace, et al 2011). Another mechanism which involves protein transporters helps in carbapenem resistance mediated by efflux pump systems (Georgios Meletis, et al., 2016) some other mechanism include periplasmic connective protein and an outer membrane porin [Schweizer, 2003]. Role of Efflux pump in resistance- active multidrug efflux pumps helps in the intrinsic resistance of a bacterial pathogen in which mutation leads to increased expression level of a given pump will inevitably result in increased resistance to all of the antibiotic substrates of that pump (Lucía Fernández, et al., 2012)

These Efflux pumps use energy in the form of proton motive force to transport various drugs and other substances out of the bacterial cell (G Meletis, et al., 2012). Quinolones, penicillins, cephalosporins and aminoglycosides are common efflux pump substrates [Meletis et al. 2012]. Due to

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the production of beta-lactamases, resistance caused by enzyme is seen in carbapenems which results in its inactivation (Timothy R Walsh, 2010) Some environmental factors that leads to the temporary activation of resistance to some antibiotic. (Lucía Fernández, et al., 2012)

All beta-lactamases are categorized into four molecular classes [Ambler, 1980]. Class A enzymes KPC [Rapp and Urban, 2012], IMI/NMC-A [Walther-Rasmussen and Høiby, 2007], SFC-1 [Henriques et al. 2004], the class B MBLs IMP [Zhao and Hu, 2011], NDM [Nordmann et al. 2011], SPM [Rossi, 2011], GIM [Castanheira et al. 2004], SIM [Lee et al. 2005], AIM [Yong et al. 2012], DIM [Poirel et al. 2010], and several class D (OXA-type) enzymes (Walther-Rasmussen and Høiby, 2006) can hydrolyze at least partially a carbapenem antibiotic. KPC, VIM, IMP, NDM and OXA-48 types are the most functional carbapenemases in carbapenem hydrolysis and also the geographical distribution. [Poirel et al. 2012].

5. Enzyme-mediated resistance to carbapenems

Beta-lactamases causes enzyme-mediated resistance in carbapenems. They are able to restrict carbapenems with other beta-lactam antibiotics and so are called as carbapenemases (Walsh, 2010). This resistance mechanism is a big threat because these enzymes inactivate the majority of β-lactams and are encoded by genes which are capable of horizontally transferred to other bacterial species. (Ann A Elshamy, et al., 2020). This type of resistance is of high importance they confer high levels of carbapenem minimum inhibitory concentrations (MICs) (Walsh, 2010).

Carbapenemase enzymes difference is clinically significant because hydrolysis profile is different and their species distribution and worldwide epidemiology is also different. (Patrice Nordmann, 2018) Ambler class A ß-lactamases: Class A carbapenemases include K. pneumoniae carbapenemases and SME, NMC, IMI, GES. KPCs are capable of hydrolyzing all β-lactams and strains carrying the blaKPC gene normally resistant to other antimicrobials (Djahmi N, et al., 2014). KPCs have a broad-spectrum activity with extended activity to carbapenems. The most frequently reported of which are KPC-2 and KPC-3, (KPC enzymes are currently the most clinically-significant enzymes among the class A carbapenemases worldwide) (Ann A Elshamy, et al., 2020: Pfeifer Y, et al., 2010)

The first time KPC producer was identified in 1996 on the Eastern coast of the USA (H Yigit, et al., 2001) and within a few years, they were identified in almost all over US. They spread worldwide and have been identified in many Gram-negative species, even though KPC enzymes are still mostly identified in K. pneumonia (Ryan S. Arnold, et al., 2012) In India, KPC-producing isolates are less common, the most common carbapenemases are NDM and OXA-48-like enzymes (P.Nordmann, et al 2014),

Ambler class B ß-lactamases: MBLs, which are known to be innate in many environmental and opportunistic bacterial species (P.Nordmann, et al 2014). Metallo-beta lactamases including IMP, VIM and NDM ß-lactamases, MBLs are known to hydrolyze all ß-lactams except aztreonam (Timothy R Walsh, et al., 2005) However, since the early 1990's, they have also been identified as acquired enzymes. Most clinically-significant carbapenemases is NDM-1 (New Delhi metallo-ß-lactamase) identified coincidentally in 2009 in K. pneumoniae and E. coli isolates from a patient in Sweden previously hospitalized in India (D Yong, et al., 2009). Ever since NDM-1 is found, its eight variants of this enzyme have already been published (NDM-1 to NDM-8) most of them originated from Asia. (L Dortet, et al., 2014) prolonged persistence of NDM producers in the human gut may result to human-to-human transfer (L Poirel, et al., 2011).

Ambler class D ß-lactamases: The third group consist of many oxacillinase OXA-48 derivatives. also named OXAs for 'oxacillinases', now include >400 enzymes, (P Nordmann, et al 2011) They hydrolyze penicillin and 1st generation cephalosporins, CHDLs show weak carbapenemase activity Finally, they do hydrolyze carbapenems although at a low level. (L Poirel, et al., 2011).

6. Carbapenem resistance among infants and pregnant women.

Carbapenem-resistant Enterobacteriaceae (CRE) have emerged as a worldwide problem; they have been seriously associated with the widespread use of antibiotic (Beatriz Suay-García, et al., 2019) Also by prolonged and acute-care hospitalization (Mckinnell J. A, et al 2019) and they have also spread to endemic areas (Hsin-Yu Chen, et al., 2021) The spread of CRE in communities is seen as a major public health threat because CRE infections have limited treatment options and increased mortality rate (Beatriz Suay-García, et al., 2019)

The rate of CRO infections has greatly seen increased in the last few years in India and around the world, representing a major public health problem. These infections are difficult to treat, leading to

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high rates of mortality (David Aguilera-Alonso, et al., 2020). The evaluation of risk factors for developing a CRO infection may permit individualized empirical broad-spectrum antibiotic therapy, according to the local epidemiology. Clinical evidence regarding the treatment of CRO infections remains scarce, and it mainly comes from observational studies, very limited in children (Jesús Rodríguez-Baño et al., 2018). New antibiotics trials which is leading to off-label use in this population. Antibiotic stewardship programs remain a key element in preserving current antibiotic activity through a rational approach to antimicrobial treatment. (David Aguilera-Alonso, et al., 2020)

Treatment options for infected children and pregnant women are less because of their week immunity therefore they are more likely to catch polymyxin-resistant infections (John Osei Sekyere, et al., 2020). Strict infection control practices in neonatal are need of an hour like antibiotic stewardship, periodic rectal and vaginal screening to forestall future outbreaks and deaths (Reenu Thomas, et al.,2019). Carbapenem resistance is common in GNB isolated from infants and pregnant women, with high resistance rates and diverse carbapenemases globally, carbapenem-resistant A. baumannii outbreaks were reported by Lee et al. 2018 (Sultan, A. M et al.,2018) *E. coli* neonatal infections and outbreaks was documented in Japan with an IMP-11 carbapenemase (Zhao, et al., 2012). New Delhi metallo-β-lactamase (NDM)–positive isolates in infants have been found in China and India, while OXA-48–positive isolates in Africa (John Osei Sekyere, et al., 2020) As colonization in pregnant women is a major risk factor for neonatal infections and outbreaks therefore there is an urgent need of infection control interventions to prevent further outbreaks and save lives.

It is seen that treatment of CR/PR-GNB infections is possible with polymyxins, higher doses of carbapenems combinations however polymyxin B appears to be a better treatment option (Reenu Thomas, et al., 2012) such treatment protocols and medicines must be distributed to all pediatricians and enforced to reduce infant mortalities worldwide specially developing countries. *(John Osei Sekyere et al. 2020)*

7. Percentage of resistance in India and global scenario.

Carbapenems are largely used especially for treatment of nosocomial infections (Krisztina M. Papp-Wallace, et al., 2011) Their use for treatment of infections caused by members of Enterobacteriaceae family has increased as the resistance of later to extended spectrum cephalosporins surfaced during 1990s. IMP-1 was the first carbapenemase reported in 1991 in Japan (Watanabe M. et al., 1991) (Georgios Meletis, 2016). VIM-1 was reported in 1997 in Verona, Italy [Lauretti et al. 1999] (Georgios Meletis, 2016). Considering the density of population of developing countries like that of India the ability of the organisms to disseminate through the intestinal flora of healthy carriers these countries can face a higher risk of transmission (Susanne Straif-Bourgeoi, et al., 2014). NDM gene was significantly more prevalent in E. coli than K. pneumoniae in India (Namita Jaggi, et al., 2019)

Overall imipenem resistance among CRE in the present study ranged from 22.9-32.9% whereas meropenem resistance ranged from 22.9-33.1% during the five-year study period. Meta-analysis of data from Asian countries demonstrated imipenem resistance varying from 0.1-5.8% and meropenem resistance varying from 0.9-2.9%. Meropenem resistance from India in this study was found to be 2.6% in one of the study, As per WHO Global report on antimicrobial resistance surveillance, two regions from 71 World Health Organization (WHO) member states reported carbapenem resistance in Klebsiella sp. in excess of 50%. (Chirag Manojkumar Modi et al. 2021) Researchers in an Indiaa at have identified strains of hypervirulent, carbapenem-resistant Klebsiella pneumoniae with high mortality rates the most common carbapenem-resistance gene found in the isolates was blaNDM. (Chaitra Shankar, et al., 2018)

8. Global spread and Reasons for the emergence and spread of carbapenem resistance

The high rate of increasing cases of carbapenem resistance as well as carbapenem-resistant Enterobacteriaceae into the community is an emerging havoc to public health (Francis S. Codjoe, et al., 2018). Despite of the large efforts being made to control this public health threat; it is very essential to look for some concrete solution. (Ann A Elshamy, 2020) Immunization can be used to minimize the spread of resistance, application of infection control measures, rationalization of antibiotic usage, proper screening and treatment, and education and awareness programs will also be a great help to minimize the burden. (Bilal Aslam et al. 2020) Greece, Italy, Brazil and China, including countries like U.S. and Colombia, have high rate of CRE. Indian subcontinent also has a high burden of CRE caused by NDM-producing strains. (Dalal Hammoudi Halat, et al., 2020). CRE rates among K. pneumoniae are as high as 62% in Greece and 33% in Italy. (ECDC- 2014-2015) In the U.S, 11%

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of K. pneumoniae causing healthcare-associated infections were resistant to carbapenems in 2014, representing a modest decline from 2013 (13%) (Lindsey M Weiner, et al.,2016), CRE cases are concentrated in the Mid-Atlantic, the Midwest and the Southeast according to the study done by *Alina lovleva in 2017.*

From few decades' emergence of carbapenem resistant bacterial pathogens which are the broadest spectrum agents of the β-lactam group, has become apparent as a worldwide public health issue. (Shio-Shin Jean, et al., 2015). Till now the most effective carbapenemases seen in terms of its hydrolysis action and geographical spread, are KPC, OXA-48, and the MBLs VIM, IMP, and NDM (Dalal Hammoudi Halat, et al., 2020) Acquired resistance in bacteria is of great concern because some of them show resistance to more than one antimicrobials. Resistance that develops due to chromosomal mutation is termed vertical evolution. (Tenover FC, 2006; Ann A Elshamy, 2020). Genes that undergo resistance are carried highly motile genetic elements which replicates and passes between bacterial cells and species, this is a major reason and mechanism by which AMR spreads in bacterial population (Ann A Elshamy, 2020). As the antimicrobial resistance worsens, significance of carbapenem in gram-negative pathogens emerges as a special clinical havoc, carbapenems are considered the most active and potent agents against multidrug-resistant (MDR) gram-negative pathogens. (Yohei Doi et al, 2019)

9. Global Epidemiology of carbapenem resistant pathogens.

Carbapenem resistance in gram-negative bacteria has caused a global epidemic that is continually growing at very high rate. Resistance was first reported in the early 1990s (Patrice Nordmann, et al., 2019) There is increased awareness of the impact of carbapenem-resistant nonfermenting gram-negative bacteria. Patients infected by carbapenem-resistant pathogens have shown increased mortality rate and low immunity compared with those infected by susceptible pathogens (van Duin D, et al., 2013).

With nonfermenters are the most highly dangerous pathogens, the overall burden of disease caused by carbapenem-resistant pathogens is similar in most regions like Asia-Pacific, the Indian continent, Europe, America (Patrice Nordmann, 2019)

In US 44.8% of baumannii and 14.2% of P. aeruginosa isolates were carbapenem resistant (Cai B, et al., 2016) Nonfermenters show higher rate of carbapenem resistance when compaired to fermenters. 44.8% of A. baumannii and 1% of Enterobacteriaceae, (Patrice Nordmann, 2019) Rate of CR by pathogen differ depending on the site of infection (Cai B, et al., 2017). At genomic level mechanism of resistance and susceptibility of the pathogen are both kept in consideration when choosing the appropriate antibiotic (Patrice Nordmann, et al., 2019)

Carbapenem-resistant Enterobacteriaceae is very much dependent on region but K. pneumonia shows highest rate in all regions studied (Alina Iovleva, et all., 2017). Regions like Greece, Italy, Brazil and China, U.S and Columbia show high rate of CRE all over region. (ECDC Surveillance report, 2014). In Indian subcontinent CRE infections due to NDM-producing strains have been reported due to community interaction whereas in all other countries infection is spread mostly during hospitalization (Borah VV, ET AL., 2016), In European and African regions OXA-48-producing Enterobacteriaceae are reported largely (Poirel L, et al., 2012)

10. Reasons for the emergence and spread of carbapenem resistance

CRE infection in humans can spread through UTI, during certain surgeries, through lungs etc. most of the time patients undergoing prolonged exposure of healthcare suffers with CRE infection (Hayden Z, et al., 2021) From last 10 to 20 years' tuberculosis was well treated by antituberculosis agents but now the effect is insufficient. Now we are capable of treating only half of multidrug-resistant tuberculosis with the present drugs (World Health Organization, 2014) Present situation is worse due to less drugs with new formula which are highly active against these multidrug-resistant Gram-negative bacteria, especially against those producing carbapenemases (Boucher et al. 2013). The comorbid person or person with week immunity when travels to the area highly infected by CRE, is at high risk to catch the disease, old age people are also at high risk (Hayden Z, et al., 2021)

Uncontrolled progression of the health problem or disease results to more immunocompromised state are the main cause of CRE infection when even antibiotics don't work. (Hayden Z, et al., 2021). There are data recorded which show direct relation between the use of antibiotics and CRE resistance. Those regions which consumes antibiotics at high rate shows high resistance (Goossens et al. 2005; Riedel et al. 2007).

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Antimicrobial stewardship and infection control can show some promising results to preventive efforts to stop or minimize the emergence and spread of carbapenem-resistant Enterobacteriaceae (Beatrice Tiri, et al., 2020). Educational campaigns can be arranged to teach healthcare professional and patient on how to limit the use of antibiotic. Proper guidelines, educational sessions and broadcast of guidelines and knowledge on proper use of antibiotics on TV, radio and social media etc can make a great difference. (Carl Llor, et al., 2014), (Beatrice Tiri, et al., 2020). The condition during present situation is worse, COVID-19 is now a global threat since February-march 2020, the same condition of less knowledge and awareness became a major problem and cause of spread of COVID-19. Separate ICU were made for COVID-19 patients they became a breeding ground for CRE and healthcare professionals were also under great pressure. (Beatrice Tiri, et al., 2020) Good habits like hand hygiene, less physical contact, healthcare personnel education, minimizing device use and so on are recommended in the guidelines published in USA and Europe for interventions to control CRE transmission in health care facilities. (Centers for Disease Control and Prevention, 2009: 2012).

All antibiotics have shown resistance over the period of time, CRE is not only the case and human habits and some medical practices leads to this issue every time (Georgios Meletis, et al.,2016) The application of antibiotics for the increase in rate of animal growth in the agricultural sector is also a major concern in stopping resistance to antibiotics, which in turn is consumed by human (Elizabeth Barclay, 1998: Georgios Meletis, et al.,2016)

11. Correlation between antibiotic consumption intensity and carbapenem-resistant gram-negative bacteria

The carbapenem resistant of gram negative bacteria is directly proportional to antibiotic consumption, the improper of usage of these antibiotics leads to resistance (Ping Yang, et al., 2018). Due to its broad antimicrobial spectrum carbapenem is highly used to treat many bacterial infections as a last resort due to which it is becoming resistant day by day (World Health Organization; 2017).

In a study 153 hospitals took part to compare the correlation between antibiotic consumption intensity and CRE and they found that, carbapenem consumption intensity and its resistant rate of the four Gram-negative bacterial strains is directly proportional to each other and are correlated (Ping Yang,et al., 2018)

A study conducted in Italy including many healthcare centers also found positive correlation between the carbapenem resistance of E. coli and third-generation cephalosporin and penicillin consumption (Agodi A, et al., 2015). Meropenem use was also studied in relation with CRKP, its consumption was increased and found that it is positively correlated with the rate of CRKP (Joseph NM, et al.,2015).

The studies are continuously proving that rapid spread of MDR bacteria in hospitals is a global health challenge (Barchitta M, et al 2020). There are many factors that leads to this problem, the use of antibiotics without knowledge is major concern and leads to resistance (WHO,2020). Increasing resistance may result in the increased consumption of several so-called “last-line” antibiotics, such as carbapenem consumption, seen usually in case of E. coli, K. pneumoniae, P. aeruginosa and A. baumannii, which cause the life threatening infections among critically ill and individuals with week immunity (World Health Organization,2017)

12. **Correlation between the mechanism of resistance and geographic location**.

Carbapenem resistance mechanisms are different in different reagions. The rates of carbapenem resistance were consistently seen higher in nonfermenters (Patrice Nordmann, et al., 2019). The spread of carbapenemase producers in A. baumannii, mostly in patients hospitalized in the ICU in seen. Carbapenemase types in Enterobacteriaceae are mostly seen in hospital-acquired pathogens mostly K. pneumoniae and spread of OXA-48 in community-acquired Enterobacteriaceae (mostly E. coli), reported in Europe. (Patrice Nordmann, et al., 2019).

In southeast Asia carbapenemases which are dominant are NDM and other MBLs and OXA-48–type (Suwantarat N, et al., 2016). In India and neighboring countries with the help of survey it is found that NDM in Enterobacteriaceae and OXA-23 are most dominant carnapenemase found in this region (Hsu LY, et al., 2017) In a survey done in many countries of Europe, E. coli were confirmed to possess a carbapenemase gene, with KPC seen 42% and OXA-48- 38% carbapenemases are reported most frequent (Grundmann H, et al., 2017). In a survey done in North American regions half of the CRE are found to be CPE, CDC conducted a survey based on population in which seven communities participated reported that 47.9% of CRE isolates were confirmed as CPE (out of which all were KPC) detected by PCR (Guh AY, et al., 2015).

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A Canadian based survey for five years was done in which every year the most dominant carbapenemases found were 66% KPC-type and NDM-1 17.3%, with increase in S. marcescens enzyme family carbapenemase and OXA-48 was also reported (Mataseje LF, et al., 2016). In Mexico a study done in hospitals reported dominance of IMP and GES enzymes in carbapenem-resistant P. aeruginosa and some of the strains had simultaneous multiple mechanisms, such as MBLs show minimum inhibitory concentrations (López-García A, et al., 2018). In hospitals in Mexico Carbapenem-resistant K. pneumoniae expressed KPC was most dominant in 2011 to 2015 (Bartolleti F, et al., 2016).

The mechanism of resistance varies according to geographic location and the selection of testing method should be based on it. Rapid diagnostic tests should be done to take effective infection control measures. National survey data, regional data and local healthcare facilities data should be used until hospitals have robust methods (Patrice Nordmann, et al., 2019)

13. Role of Carbapenem Resistance Colonization

Some studies suggested that Carbapenem resistance transportation was a significant risk factor for CR BSI occurrence in Patients with Hematologic Malignancies (Andria et al., 2015; Trecarichi et al., 2016; Jaiswal et al., 2018). In a study in Italy, the rate of CR-bacteria colonization among HM patients during hospitalization reported 3.8%, Indian group reported 20% of patients acquired CR colonization in hospital (Rym Lalaoui, et al., 2020). In another study, 18% of CR-colonized patients developed CR-bacteria BSIs, (Jaiswal et al., 2018). It was found that mostly AML causes the strong risk for maximum cases of CR-bacteria colonization (Ballo et al., 2019).

CR-Enterobacteria positive patients should be kept in strict nursing care precautions, they should be provided one to one care in separate rooms and healthcare staff with minimum contact. (Centers for Disease Control, 2019). At the time of diagnosis and chemotherapy, gut colonization was checked (Ballo et al., 2019) (Rym Lalaoui et al., 17 July 2020) In a study 152 pediatric patients were observed who were undergoing liver surgery, their Anal swab was take before and after entering ICU to study intestinal CRE colonization. 28.9% patients shown CRE intestinal colonization out of which 11 % cases were found after ICU stay (Yan Sun, et al.,2021)

Patients admitting with serious illness in the intensive care unit (ICU) particularly faces high burden of CRE infections due to colonization of infection in ICU and also show high risk of death (Tischendorf J, et al., 2016). Human intestine is a major reservoir of CRE, Enterobacteriaceae commonly colonize in this area in human body and Colonization with CRE is a main cause of CRE infections (Thomas Howe McConville, et al., 2017).

14. **Antimicrobial susceptibility testing and Carba NP testing**

Susceptibility testing methods- It is known that Laboratory detection of resistance to carbapenems is becoming very difficult for many reasons, the use of automated methods for identification and susceptibility testing in addition to the lack of standardized methods for detection (Hanan Ahmed, et al., 2009) Antimicrobial susceptibility testing is done to confirm susceptibility to chosen antimicrobial agents. Macrobroth or tube-dilution method is one of the oldest antimicrobial susceptibility testing method (Ericsson JM, et al., 1971), The antimicrobial gradient diffusion method to determining susceptibility (Citron DM, et al.,1991). The disk diffusion susceptibility method (Bauer AW, et al., 1996). An instrumentation Method-Automated instrument systems, it can give accurate results by the reading of end points and give susceptibility test results in a shorter period than manual readings.it has four types, where 3 of them are rapid susceptibility test and one gives overnight results (Richter SS, et al., 2007). MicroScan WalkAway, The BD Phoenix Automated Microbiology System, The Vitek 2 System (bioMérieux) and he Sensititre ARIS 2X (Trek Diagnostic Systems are the 4 types of Automated instrument system used for susceptibility testing. (Hanan Ahmed, et al., 2009)

Many laboratories use automated systems like MicroScan for quick identification and susceptibility testing of isolated bacteria. (Richter SS, et al., 2007) These systems have many advantages including testing large number of clinical specimens and decreasing the in-laboratory turnaround time. similar to disk diffusion. The sensitivity and specificity of disk diffusion method could not be calculated for two reasons First, it was the reference method. Second, sensitivity and specificity of disk diffusion method could not be calculated due to unavailability in our laboratory of other gold standard methods like agar dilution or microdilution (Barenfanger J, et al.,1999) (Richter SS, et al., 2007).

There are International agencies which determine the Minimum inhibitory concentrations (MICs) of all antimicrobial susceptibility testing (AST), they decide the guidelines of to determine antibiotic is

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susceptible (Kassim A, et al., 2016). Due to the rapid increase in antibiotic resistance there is a need to develop technologies that will permit rapid AST (within an hour) and are non-invasive. (Zeeshan A. Khan, et al., 2019).

Carba NP test- The Carba NP test is a rapid colorimetric test, based on pH changes that accompany hydrolysis of imipenem by carbapenemases (Nordmann P, et al., 2012). It is highly sensitive in detecting KPC and most MBL-producing strains (Tijet N, et al., 2013). Carba NP test is very useful for early detection of carbapenemase production in Enterobacteriaceae and some others as recommended by (CLSI, 2015). (Dortet L, et al 2012). Carba NP test have some advantages over other tests because it quick results, it is very simple to perform the test, it gives very specific results and objectiveness in interpretation (Dortet L, et al., 2014). Carba NP test was modified and the modified version gave better results when done using cell extracts obtained by probe sonication, bath based sonication is less expensive than probe in this method and it also prevents environment contamination (Eloiza H. Campana, et al., 2017).

Conclusion

Uncontrolled progression of the health problem or disease results to more immunocompromised state is the main cause of CRE infection when even antibiotics don't work.There are data recorded which show direct relation between the use of antibiotics and CRE resistance. Those regions, which consumes antibiotics at high rate, shows high resistance. Antimicrobial stewardship and infection control can show some promising results to preventive efforts to stop or minimize the emergence and spread of carbapenem-resistant Enterobacteriaceae. Educational campaigns can be arranged to teach healthcare professional and patient on how to limit the use of antibiotic. Proper guidelines, educational sessions and broadcast of guidelines and knowledge on proper use of antibiotics on TV, radio and social media etc can make a great difference. The condition during present situation is worse, COVID-19 is now a global threat since February-march 2020, the same condition of less knowledge and awareness became a major problem and cause of spread of COVID-19. Separate ICU were made for COVID-19 patients they became a breeding ground for CRE and healthcare professionals were under great pressure. Good habits like hand hygiene, less physical contact, healthcare personnel education, minimizing device use and so on are recommended in the guidelines published in USA and Europe for interventions to control CRE transmission in health care facilities.

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