A review of Carbapenems Resistance in the Current World

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Abstract

Carbapenems are a subgroup of beta-lactam antibiotics, which have been effective in treating Gram-negative bacteria. These groups of drugs are particularly effective for resistant Gram-negative bacteria that are multi-drug resistant mainly to all types of penicillins and cephalosporins. It is a reality now that there is a looming crisis due to emergence of resistance to these groups of drugs. Efforts to fight resistance is by new therapies that are combining cephalosporins with inhibitors such as vaborbactam, avibactam and relebactam. However, already resistance has been noted against ceftazidime-avibactam according to recent studies. The effectiveness of carbapenems has gone down due to beta-lactamases, production of efflux pumps and target modification. Commonly encountered carbapenemases conferring resistance to this group of drugs include KPCs (*Klebsiella pneumoniae carbapenemases*), which are class A beta lactamases, NDMs, in full New Dehli metallo-β-lactamases, VIM (Verona Integron encoded metallo-β-lactamases), IMPs (Iminpenemases) which are class B metallo-β-lactamases and OXA-48 (oxacillinases) which are Class D β-lactamases. This review gives a global distribution overview and the evolution of carbapenemases, which are spreading at a fast rate. There are measures to overcome this menace such as enhancing infection prevention control (IPC) measures. Another approach is implementing and upholding diagnosis and antibiotic stewardship especially in Low-middle-come-countries (LMICs).

Key words: Carbapenems resistance, Antimicrobial resistance, Carbapenem-resistant Enterobacterales, Beta lactamases

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Introduction

Challenge of Antimicrobial Resistance

Resistance to antimicrobials has been described as a natural process that has been present since time immemorial. The genes responsible for drug resistance in some strains of bacteria can be dated before antibiotics discovery by millions of years. Despite the genes being in existence long before antibiotic discovery, overuse of antimicrobials has been attributed to the increased rate of emergence and spreading of antimicrobial resistance (AMR)(Review on Antimicrobial Resistance, 2016). The development of new drugs to treat these new superbugs is lagging (Review on AMR, 2014).

It is estimated that more than 700,000 people die yearly from multi-drug resistant strains of common bacterial infections, HIV, TB, and malaria. This estimate is likely to be an underrate because of poor reporting and surveillance of AMR especially in the developing world (Review on Antimicrobial Resistance, 2016). In India, neonatal infections caused by antibiotic-resistant microorganisms cause the deaths of approximately 60,000 newborns each year (Laxminarayan et al., 2013).

It is now evident that carbapenem-resistance carrying organisms are spread across geographical regions and are causing significant mortality and morbidity (Martin et al., 2018). Carbapenem-resistance proportions in some European and Asian countries are now already above 50%. In the US, infections with *Klebsiella pneumoniae* carbapenemases (KPC)-positive bacteria are a public health concern, with every state in the US now reporting infections with KPC-expressing *K. pneumoniae* (Hansen, 2021).

Carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and carbapenem-resistant *Acinetobacter baumannii* (CRAB) are now enlisted in the 2017 World Health Organization (WHO) global list of priority pathogens.

There is a deduction that is founded on the trend of rising drug resistance for six pathogens by 2050, the deaths from antimicrobial resistant pathogens could reach 10 million lives each year-by-year 2050. The total cost is estimated at 100 trillion USD if no action is taken (Review on AMR, 2014). The death toll is thus deducted to be astounding one person every three seconds (S. C. Davies et al., 2013).

Immediately after World War II, there was a 'golden era' whereby antibiotic innovation was rampant in 1940 up to thirty years later (J. Davies, 2006). The rate, though, of discovery has reduced significantly since 1980 (Payne et al., 2006). Very few new antibiotics have been discovered. Technology advancement, which was very promising at that time failed in delivery of new antibiotics (Renwick et al., 2016).

There has been reduced investment capital channeled into antibiotic discovery research despite the rise in AMR (Kinch et al., 2014). There has been limited funding on the area of AMR with National Institute of Health NIH allocating 1.2 percent of its grant funding to AMR-related research between 2009 and 2014. This is a very minute share compared to 18.6 percent which is more than five billion USD yearly to cancer research. The European based Joint Programming Initiative on AMR (JPIAMR) as an organization has tried to overturn this disturbing trend by helping to channel more public funding into AMR research (Zorzet, 2014).

Description of carbapenems

Carbapenems are bactericidal beta-lactam antibiotics which act by binding to penicillin-binding proteins (PBPs) and are closely related to penicillins (Kong et al., 2010). They bind and inactivate these proteins thus inhibiting the crosslinking of

the bacterial cell wall, which leads to cell death. They contain a fused B-lactam ring and a five membered ring system that is quite different from penicillin. It is unsaturated and contains a carbon atom instead of sulphur (Papp-Wallace et al., 2011). Carbapenems have a broader spectrum in terms of activity than most beta-lactams. They differ from other classes of B-lactams in their precise chemical structure. Their use has increased as a result of the increasing resistance to cephalosporin antibiotics in Enterobacteriaceae which includes *Escherichia coli*, *Klebsiella*, *Enterobacter*, *Proteus* and others.

Carbapenems have been proven to have activity against extended spectrum β-lactamase (ESBL) producing bacteria (Baughman, 2009). Types of carbapenems include imipenem, meropenem, doripenem, ertapenem, panipenem and biapenem.

Usage of carbapenems

Carbapenems have been used empirically for serious infections with shown benefit by several studies (Baughman, 2009). They are also a second line drug of choice when the first line is insufficient (Colardyn, 2005). There are increased death rates for patients with VAP (ventilation acquired pneumonia) when the patients have received inadequate initial antibiotics (Kollef, 2000; Luna et al., 1997). This prompts the use of antibiotics with a wider spectrum that cover for all potentially resistant bacteria in the patient with suspected VAP (Cavalcanti et al., 2005; Kollef et al., 1999; Patel et al., 2002; Safdar et al., 2005). The use of carbapenems with or without aminoglycosides and fluoroquinolones is highly recommended (American Thoracic Society, 2005).

Urinary tract infections are one of the most common nosocomial infections (NNIS report, 2004). These infections are not life threatening as other nosocomial infections but still represent a major cause of illness. They are a source of multidrug resistant organisms, especially gram-negative rods. Fluoroquinolones are commonly used as first-line therapy for UTI, but resistance has been established with *Escherichia coli* and *P. aeruginosa* urinary isolates (Zhanel et al., 2006). The carbapenems have thus being in use against these MDR bacteria.

Carbapenems have been effectively used for intra-abdominal infections (IAIs) which is a common complication seen post-surgery (Toniolo et al., 2006). Most of these times, the causative agents for these infections include multidrug resistant gram-negative bacilli and methicillin resistant *Staphylococcus aureus* (NNIS report, 2004; Toniolo et al., 2006). Patients suffering from IAIs sometimes also develop a nosocomial super-infection. Longer hospital stays and higher mortality is attributed by nosocomial infections (Merlino et al., 2004). An important reason for nosocomial super-infection is insufficient initial empiric antibiotic administration. Carbapenems have been recommended for many other infections which include complicated skin and soft tissue infections (Stevens et al., 2005), meningitis (Tunkel et al., 2004) and septicemia (Reddy, 2022). They have been indicated largely for use against *P. aeruginosa* and other gram-negative rod infections in patients with cystic fibrosis.

Carbapenem resistance

Resistance to carbapenems is mainly as a result of production of carbapenemases. Other mechanisms include porin-mediated resistance that decreases uptake of carbapenems and efflux pumps, which pump the carbapenem to the external environment of the cells. Enzyme mediated resistance is dependent on microorganisms acquiring genes that produce carabapenemases. Carbapenemases are thus classified beta-lactamase's (Bush & Bradford, n.d.).

Porin loss and alterations in outer membrane proteins (OMPs) combined with the activity of ESBL or AmpC B lactamases is a significant mechanism of resistance. Chromosomally encoded and plasmid mediated enzymes hydrolyse carbapenem antibiotics and typically also most other B lactams and other B lactamase inhibitors. There are two types of carbapenemases divided into two molecular groups namely metallo-carbapenemases and serine carbapenemases. They are distinguished by hydrolytic mechanisms at molecular level (Codjoe & Donkor, 2017).

The metallo-betalactamases are inhibited by Ethylene Diamine Tetraacetic acid (EDTA) and contain at least one zinc atom at the active site. Serine carbapenemases contain serine at the active site and are susceptible to clavulanic acid and tazobactam, but not to EDTA (Queenan & Bush, 2007) **(Table 1).**

Class A carbapenemases constitute the SME (Serratia marcescens enzyme), IMI (imipenem hydrolyzing betalactamase), GES (Guiana extended spectrum) and KPC. Class B carbapenemases constitute GIM (German imipenemase), SPM (Sao Paulo MBL), NDM, VIM, IMP, SIM (Seoul imipenemase), whereas class D includes OXA (oxacillinase) and OXA-48.

The main family of class A serine carbapenemases are the KPC enzymes (Jeon et al., 2015).

Table 1: Principal characteristic of the carbapenemases, grouped according to Ambler classification.

MOLECULAR CLASS	A	B	D
Functional Group	2f	3	2d
Active Site	Serine	Zn^{++}	Serine
Aztreonam Hydrolysis	+	-	-
Edta Inhibition	-	+	-
Apba Inhibition	+	-	-

KPC-type

KPC refers to *Klebsiella pneumoniae* carbapenemases, a type mainly found in *Klebsiella pneumoniae.* These carbapenemases are serine carbapenemases and functional group 2f (Ambler class) and therefore they inactivate different antimicrobial drugs such as aminoglycosides, fluoroquinolones. They also have activity against β- lactams including penicillins, carbapenems, cephalosporins, and aztreonam (Navon-Venezia et al., 2017). They are inhibited by clavulanic acid and tazobactam (Papp-Wallace, 2019).

There are several types of KPC variants namely KPC-2 to KPC- 17 (Ribeiro et al., 2016). Though KPCs are mainly found in *K. pneumoniae*, they have also been found in *Salmonella species* (Arnold et al., 2011) and *Escherichia coli* (Hirsch & Tam, 2010). Other species found to harbor KPC *include Pseudomonas aeruginosa* and *Acinetobacter baumannii* (Robledo et al., 2011). KPC infections are associated with more deaths for patients than that caused by carbapenem susceptible organisms.

VIM-type

VIM stands for Verona-intergron-encoded metallo-β-lactamase. It is a metallo-β-lactamase that belongs to the Ambler Molecular class B (Aquino-Andrade et al., 2018). VIM inactivates carbapenems and extended-spectrum beta-lactams. They are not inhibited by clavulanic acid, sulbactam and tazobactam (**Table 1**) (Pandey & Cascella, 2023). This metallo-β-lactamase has been shown by several studies to spread rapidly (Martinez-Freijo et al., 1998).

IMP-type

IMP type metallo-betalactamases were first isolated in Japan. There are approximately 50 IMP-like variants. They are widespread globally and mainly harboured in transposons and plasmids. They have been isolated from *P. aeruginosa, K. pneumoniae* and *S. marcescens* (Jin Hong et al., 2015). They induce strong resistance against carbapenemases (Meletis, 2016).

OXA-type

The oxacillinases are widespread globally. Oxacillin-hydrolyzing enzymes (OXA) are class D serine beta-lactamases (Fig 1.1). There are 200 types of OXA enzymes that are known. In a few cases, they are responsible for low levels of resistance to carbapenems (Antunes et al., 2014). OXA-48 is unique in that it is found in a plasmid and is common in the family of *Enterobacteriaceae*. It confers resistance to penicillins, β-lactams, cephalosporins and even carbapenems (Evans & Amyes, 2014; Loucif et al., 2016).

NDM-type (New Delhi Metallo-betalactamses)

It hydrolyses all carbapenems except aztreonam and monobactam. There are 16 NDM variants (NDM 1-16) (Raghunath, 2010). NDM is commonly found in *K. pneumoniae* and in *Enterobacterales* (Göttig et al., 2010; Peirano et al., 2011). NDM-1 brings resistance to most other classes of antibiotics as well.

GES (enzymes) Guiana Extended-Spectrum β-lactamase

GES enzymes inactivate broad-spectrum cephalosporins. The genes in the GES family are located on transferable plasmids and integrons (Woodford et al., 2004).

The IMI/NMC-A enzyme (imipenemase/ not metalloenzyme carbapenemase – A)

The IMI/NMC-A enzyme, mainly found in *Enterobacter* spp. have capability of inactivating carbapenems, but at the same time are susceptible to extended-spectrum cephalosporins. NMC-A are not very common in clinical settings (Pottumarthy et al., 2003; Rotova et al., 2017). The $_{bla}$NMC-A gene is chromosomally located and is inducible due to the LysR-type regulatory gene. This scenario is similar to genes found upstream of chromosomally encoded AmpC-type enzymes. They are normally located upstream of $_{bla}$NMC-A gene (Pitout et al., 2015). IMI carbapenemase, named IMI-1 was described by Rasmussen *et al*. (Rasmussen et al., 1996) and was obtained from two *E. cloacae* clinical strains.

The SME (*Serratia marscescens* enzyme) enzymes

SME is mainly found in *S. marscescens* clinical isolates (Yang et al., 1990). SME-1 and NMC-A are almost identical in their amino acid sequence. The two, NMC-A and $_{bla}$SME-1 are regulated by Lys-R type regulatory gene (Naas et al., 1995). The SME-1 has been reported together with SME-2 and SME-3 in *S. marscescens* strains (Mataseje et al., 2014).

Other acquired metallo-β-lactamases

The SPM-1 (Sao Paulo MBL) enzyme was first detected in *P. aeruginosa* (Toleman et al., 2002). The GIM-1 (German imipenemase-1) is an enzyme that was recovered from Germany (Walsh et al., 2005). SIM-1 (Seoul imipenemase) source is *Acinetobacter baumannii* detected from seven clinical isolates from South Korea (Lee et al., 2005). *Citrobacter freundii* clinical isolate were discovered to habour KHM-1 (Kyorin Health Science MBL) in Japan (Sekiguchi et al., 2008)

Pseudomonas stutzeri is the source of the DIM-1 (Dutch imipenemase) enzyme in the Netherlands (Sun et al., 2016). Achromobacter *xylosoxidans* is the source of TBM-1 (Tripolli MBL) enzyme (Kayama et al., 2014). *P. aeruginosa* is the source of AIM-1 (Adelaide imipenemase) enzyme in Australia (Yong et al., 2012).

Other enzymes that confer resistance to carbapenems include BKC (Brazil Klebsiella carbapenemase) (Nicoletti et al., 2015) which is class A, Florence imipenemase (FIM) (Class B) (Sawa et al., 2020) and *Serratia franticola* carbapenemase (SFM) which is in Class A of carbapenemase classification (Henriques et al., 2004).

Global Epidemiology of carbapenemases

USA

KPC is the most common carbapenemase in the US with a 50% related mortality rate (Kuehn, 2013; Nordmann et al., 2011). KPC enzyme spread rapidly in thirty-nine states of the

USA (CDC, n.d.). MBLs have not been commonly implicated for carbapenem resistance in Enterobacteriaceae in the US and CANADA. In unlikely cases, OXA-48-like carbapenemases are reported as a cause of carbapenem resistance in Enterobacteriaceae in the US.

Europe

There is a study that included France, the United Kingdom and 39 countries that came together to reduce the burden of carbapenems resistant *Enterobacteriaceae* in each of their countries (Glasner et al., 2013; McKenna, 2013). The first KPC gene in the UK was found in an *Enterobacter* species from a blood sample and the first case of a known *Klebsiella pneumoniae* producing KPC-positive isolate was from Scotland (Woodford et al., 2008). For *K. pneumoniae*, based on data obtained the European Antimicrobial Resistance Surveillance Network (EARS-Net), dated 2017 there is large difference in margins in the rates of carbapenem resistance in isolates from invasive infections, ranging from 0% to 64.7%. Slovakia, Poland, and Portugal have maintained increasing trends for the years between 2014-2017, while there was a decrease in Croatia, Slovenia, and Italy. Carbapenem resistant *E. coli* invasive infections were lower in terms of national percentages while compared to *K. pneumoniae.* NDM producers are most found in Romania, Poland, and Denmark.

Africa

African countries do not have active surveillance studies specially monitoring the carbapenem resistance. NDM-1 was reported in Morocco, Kenya, and South Africa (Poirel, Benouda, et al., 2011; Poirel, Revathi, et al., 2011; Rubin et al., 2014). Others described in Kenya include VIM, SPM, SIM, IMP, VEB (Vietnamese extended-spectrum beta-lactamase), OXA-48 and GIM. South Africa led amongst African countries to have first described a bacterium that harboured KPC-2 variant back in the year 2012. In Ghana, a study reported that KPC was not present in all carbapenem resistant Gram-negative bacteria tested. However, Codjoe found NDM-1 in *Acinetobacter baumannii*, VIM-1 in *Pseudomonas* species and OXA-48 in *Klebsiella pneumoniae* in Ghanian isolates (Codjoe & Donkor, 2017; Donkor et al., 2017; Duedu et al., 2017; Opintan et al., 2008). Tanzania and other East African countries have detected $_{bla}$OXA-24, $_{bla}$OXA-58, $_{bla}$IMP, $_{bla}$VIM-1, $_{bla}$SPM-l, $_{bla}$NDM-1, $_{bla}$OXA-23, and $_{bla}$KPC from various bacterial isolates (Ssekatawa et al., 2018).

Carbapenems resistance in children aged under 5 in Africa.

Resistance to carbapenems has been already reported in children under 5 in various African countries which include Nigeria (Brinkac et al., 2019), where it was reported in neonatal sepsis cases, in South Africa where it was evidenced in children with HIV/AIDS amongst other cases (Ballot et al., 2019; Malande Oliver Ombeva & u Plessis Annerie , Rip Diane , Bamford Colleen, 2016; Ogunbosi Id et al., 2020) and in Kenya where it was characterized in asymptomatic gastric carriages cases (Mutuma et al., 2023) Figure 1.

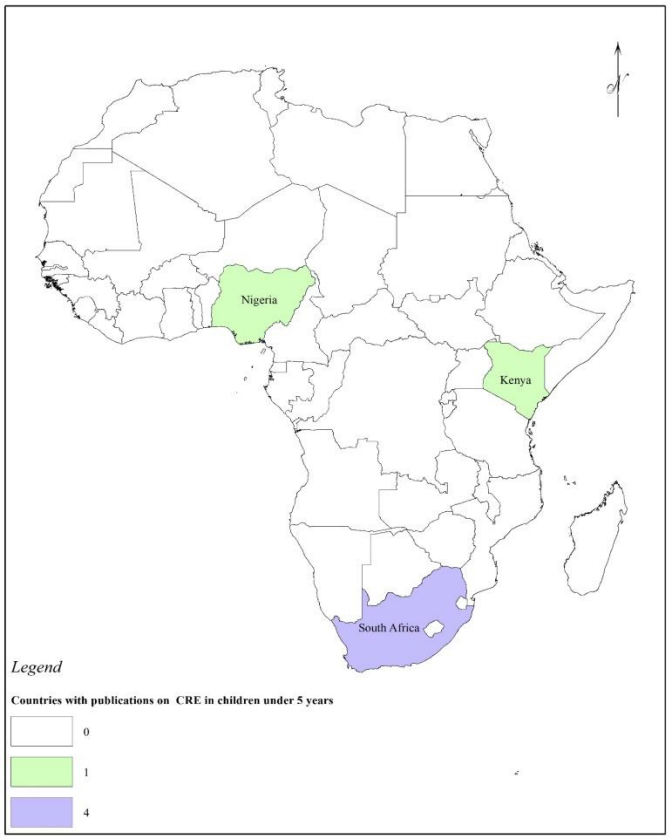

Figure1: Map of Africa indicating countries with reported carbapenem resistance in children less than 5 years

Asia/China

Several studies in the region have identified various carbapenemases. In China, *Enterobacter spp* were found to harbor NDM-1, NDM-5, IMP-4, IMP-26, IMP-1, KPC-2 and VIM-1(Jin et al., 2018). In India isolates with KPC were first described during a phase-3 clinical trial of the tigecycline drug carried out from 2002 to 2006. *Klebsiella pneumoniae*, *Proteus mirabilis* and *Escherichia coli* were found to harbour KPC gene (Kumarasamy & Kalyanasundaram, 2012). *Klebsiella pneumoniae* isolates in India were found to be co-harbour carbapenemases as well as ESBLs. The carbapenemases detected were KPC-2, OXA-1, NDM-1 while the ESBLs were TEM-1, CTX-M-15, and SHV-12 (Castanheira et al., 2011). The *K. pneumoniae* isolates also harboured RmtB, which confers aminoglycoside resistance and thus were identified as multidrug resistant isolates (Kumarasamy & Kalyanasundaram, 2012). OXA-181 was demonstrated to be the commonest genes in Indian hospitals by the SENTRY antimicrobial surveillance programme carried out (between 2006 and 2007 (Castanheira et al., 2011). *Escherichia coli* isolates that are KPC-positive have also been reported in India. Data from CAESAR, in full, Central Asian and European Surveillance of Antimicrobial Resistance

network demonstrated that countries neighboring to the Europe had elevated carbapenem resistance amongst *K. pneumoniae* in 2017. As for countries in Southeast Asia, which include Thailand, Vietnam and the Philippines, they had carbapenem resistance percentages of less than 5% for *K. pneumoniae*. Myanmar and Indonesia data for *E. coli* carbapenem resistance rates were also below 5% (Europe, 2023).

South America

Various studies have demonstrated the presence of various carbapenemases in Brazil, Colombia, and Argentina. *Enterobacteriaceae*, *Pseudomonas spp*., and *Acinetobacter spp*. are responsible for numerous infections in clinical settings in the region. In the SENTRY surveillance carried out in the region, several carbapenemases have been demonstrated from gram negative bacteria. These include OXA-48, OXA-143, NDM, SPM and IMP. VIM has been rarely described in most countries in this region. However, a novel carbapenemase has been described, Brazil Klebsiella Carbapenemase BKC-1(Nicoletti et al., 2015). *Klebsiella pneumoniae* isolates carrying KPC-2 have been demonstrated from an intensive care unit whereby the patient had no trace of travel history in 2006 (García Ramírez et al., n.d.). Thereafter, expanded studies were done in entire Brazil, including hospital wastewater surveillance, and clone type-ST437 was widely disseminated among KPC-2-positve *Klebsiella pneumoniae* isolates (Monteiro et al., 2009).

Australia

In the last few years, the prevalence of carbapenemases in this region has remained low. This can be attributed to adherence to infection control measures and consistent surveillance programmes (CDC, n.d.; Maya et al., 2014; Silvia Munoz-Price & Quinn, 2009).

Carbapenem resistance diagnosis

Laboratory detection is normally challenging due to heterogeneous expression of resistance to betalactams.

KPC chromoagar

KPC chromoagar is one of carbapenems resistance screening tests that is 100% sensitive (Maurer et al., 2015). This laboratory media contains carbapenemases in it and only microorganisms resistant to such grows on KPC agar.

Modified Hodge test

Modified Hodge Test (MHT) is a test employed in detecting KPC, Metallo Beta lactamase (MBL) and the SME-1 in *Serratia marcescens* (Amjad et al., 2011). It is a test whereby inactivation of a carbapenem by carbapenemase -producing strains (test isolate) enables a carbapenem -sensitve indicator strain (*E. coli* ATCC® 25922) to grow towards a carbapenem-containing disc along the streak of inoculum of the test strain. Positive test results are shown by cloverleaf-like indentation.

Carba NP

Acidimetry is the principle used for the Carba NP test, which was developed by Nordmann *et al*. There is hydrolysis of the beta-lactam ring results in a drop in pH, causing a color change of phenol red indicator from red to yellow (Nordmann et al., 2012). The test requires commercially purchased bacterial protein extraction reagent (BPER), phenol red indicator, zinc sulphate heptahydrate ($ZnSO_47H_20$), and standard grade imipenem powder.

Multiplex immunochromatographic assay has been used for detection of various carbapenemases (Kon et al., 2021). The 'big 5' carbapenemases that should be detected by any method include KPC, OXA-48-like, NDM, VIM and IMP. The kits are antibody antigen-based kits that use highly sensitive monoclonal antibodies.

Carbapenem Inactivation Method

In this method a suspension of bacteria is done and an antibiotic testing disk containing 10ug meropenem is placed in the suspension and allowed to incubate for a minimum of two hours at 35^0C (Tang et al., 2018). The disk is removed after incubation using an inoculation loop. It is then placed on a Mueller Hinton agar plate inoculated with susceptible *E. coli* indicator strain (ATCC 29522) and thereafter incubated at 35^0C. If the bacterial strain in suspension contains carbapenemases, it will inactivate the meropenem and allow diffuse growth of *E. coli*.

GeneXpert

It saves on time since the evaluation of carbapenemase genes directly from clinical and screening specimens is possible. GeneXpert CarbaR cartridge is relies on a multiplex real-time PCR method. The Xpert Carba-R test performs well for the big five (KPC, NDM, VIM, IMP, and OXA-48) (Traczewski et al., 2018).

Recommendations

Infection Prevention Control and antimicrobial stewardship are critical.

Carbapanem resistance is serious in both community and hospital acquired infections. Infection Prevention Control practices and judicious use of antibiotics are essential to prevent further spread of resistance. Involvement of national level stakeholders has the potential to effectively control the menace of antimicrobial resistance (Pierce et al., 2017).

Surveillance of CRE-CRAB-CRPsA (Carbapenem Resistant Enterobacteriaceae, Carbapenem Resistant *Acinetobacter baumannii*, Carbapenem Resistant *Pseudomonas aeruginosa*) infection and surveillance cultures to detect asymptomatic CRE colonization.

Screening in Low-Middle Income Countries (LMICs) of the priority organisms should follow on the local epidemiology and special attention high-risk areas such as the intensive care units (Friedman et al., 2017). It is always a challenge in Low-

Middle Income countries and thus low-cost tests can be employed due to limited resources.

Hand hygiene adherence for the control of CRE-CRABS-CRPsA

Hand hygiene practices should be according to the WHO guidelines on hand hygiene in health care (106).

Contact precautions and patient isolation.

As for patients diagnosed with CRE-CRAB-CRPsA, it is recommended that they should be cared for separately to avert spread (Magiorakos et al., 2017). In developing countries, hospital settings need to be prepared for such infrastructure.

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