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Occurrence of carbapenem-resistant organisms in gastrointestinal postoperative infections: A therapeutic challenge

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ABSTRACT

Background: Dissemination of multidrug resistant organisms including Carbapenem-Resistant Organisms (CRO) in Hospitals is of global concern. Such nosocomial infections are more common during surgical procedures involving prolonged post-operative care and Hospital stay. Treatment options include administration of prophylactic antibiotics, which are broad-spectrum antibiotics. However, long-term administration of these antibiotics leads to an increase in the incidence of multidrug resistant organisms in Hospital sectors.
Objective: To evaluate early detection of carbapenemase producing organisms from the clinical isolates of postoperative patients by carba NP test.
Materials and Methods: The study was conducted at the diagnostic laboratory in clinical samples obtained from hospitalized patients. A total of 716 clinical samples were tested by employing basic microbiological and biochemical testing methods and the isolates were screened for antimicrobial susceptibility. Carbapenem-resistant isolates were then confirmed by E-test (imipenem, meropenem) and also via carba NP test.
Results: In a total of 716 samples, 257 tested positive for various microorganisms, of which 230 gram-negative bacilli were identified. Amongst them, 93 isolates were identified as resistant to carbapenem by disc diffusion method of which 50 isolates were tested for carbapenemase production. Within the 50 isolates, 47 isolates were resistant to E-test meropenem and 40 isolates were resistant to imipenem. Of note, 35 out of the 50 CROs were identified as carbapenemase producers.
Conclusion: Our results show that Carba NP test is a simple method that can be employed routinely for early detection of carbapenemase mediated CROs thus reducing the spread of resistant strains in Hospitals.

1. Introduction

Postoperative infections are a major worldwide issue in the area of healthcare causing increased morbidity and mortality. These are nosocomial infections, that often occur within the tissues of incision and the operative area. These infections typically develop between the 5^{th} and 30^{th} day of hospitalization post-surgery, which can vary from Hospital to Hospital.[1,2] These infections may be superficial or deep. They are typically caused by exogenous microorganisms (on the surface of the host) and endogenous microorganisms that

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enter the operative area either during the surgery or post-surgery.[3] These infections may occur on all layers of the body wall leading to delayed recovery and postoperative sequelae.[2,4]Rendering antimicrobial drug(s) continuously as a treatment method during these infections has resulted in emergence of antibiotic resistant microorganisms. Hence, rapid diagnosis of the causative microorganism(s) and the appropriate antibiotic treatment(s) can reduce morbidity and mortality.

The postoperative infections like community-acquired and Hospital-acquired infections, including urinary tract infection (UTI), blood stream infection (BSI), ventilator associated pneumonia (VAP), intra-abdominal infection (IAI) and lower respiratory tract infection are commonly caused by gram-negative bacteria, specifically *Enterobacteriaceae.* These infections are generally treated using broad-spectrum β-lactam antibiotics such as cephalosporins, cephamycins and carbapenems. However, continuous treatment with such antibiotics may induce bacteria to develop resistance against the same. In addition, these bacteria can acquire genes encoding multiple antibiotic resistance mechanisms, including Extended–Spectrum β-lactamase (ESBL), AmpC β-lactamase and Carbapenemases that decreases the penetration of beta-lactam drugs. Beta-lactam drugs are typically a primary choice of therapeutics in serious infections.[3,5] Among which, carbapenem, a β-lactam antibiotic is widely considered as the last resort. This antibiotic binds to penicillin–binding proteins thereby inhibiting transpeptidases and preventing the synthesis of peptidoglycan eventually leading to cell death. Hence, administration of carbapenem antibiotics act as a broad-spectrum therapeutic option over a vast range of gram-negative microorganisms.[6] Therefore, increased use of carbapenem as a last line of treatment for infections results in increased prevalence of carbapenem-resistant *Enterobacteriaceae* (CRE) and also other non-fermenters. This increase in multidrug resistant bacteria is mostly due to inadequate infection control practices.[7,8]

Emergence and spread of carbapenem-resistant *Enterobacteriaceae* including non-fermenters are of significance in clinical and public health.[5,6] These bacteria elicit resistance by producing beta-lactamase enzymes that readily inactivate carbapenem along with other resistance mechanisms including generation of porin mutations that prevent accumulation of beta-lactam in the bacteria.[9] Primarily, inactivation of carbapenem and other beta-lactam antibiotics by the production of carbapenemase enzyme is key in causing resistance.[6] Majority of the carbapenemases were identified in *Klebsiella pneumoniae* known as *Klebsiella pneumoniae* carbapenemases (KPCs). These enzymes, however, are not limited to *Enterobacteriaceae* and can also be found in non-fermenters such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Of note, these carbapenemase producing organisms spread rapidly than other non carbapenemase producers.[10] Importantly, they can confer resistance on their own without any accompanying resistance-causing mechanisms or chromosomal mutations.[9] Hence, treatment option(s) for CRE infections remain very limited. Thus, early detection may prevent the dissemination of resistant organisms among patients and may also provide therapeutic-guidance for antibiotic treatment of the infections. Rapid diagnosis of such carbapenemase producing organisms, as a first-line screening method, can reduce morbidity and mortality. This study was set out to screen for occurrences of carbapenemase producing organisms from the clinical samples of gastrointestinal postoperative patients by employing the rapid detection carba NP test.

2. Materials and Methods

2.1. Sampling

Clinical specimens (wound pus, bile, sputum, body fluids) collected from gastrointestinal postoperative infected patients from the Institute of Surgical Gastroenterology and Liver Transplant, Government Stanley Hospital, Chennai. The collected specimens were transported to the microbiology laboratory.

2.2. Isolation and identification

The samples were inoculated on the MacConkey agar and Blood agar plate. The plates were incubated (aerobically) overnight at 37ºC. Isolates grown on culture plates were identified by its colonial, Gram staining and conventional biochemical characteristics.

2.3. Phenotypic detection of Carbapenem-Resistant organisms (CRO)

2.3.1. Disc diffusion method

A primary method for early detection of carbapenem resistance was Antimicrobial Susceptibility Test (AST). AST for the isolated pathogen was performed on the Muller Hinton Agar (MHA) by modified Kirby-Bauer disc diffusion method as per the Clinical and Laboratory Standards Institute (CLSI) guidelines. The tested antibiotics include aminoglycosides (amikacin and gentamycin), Cephalosporins (cefatoxime and ceftazidime), Carbapenems (meropenem, ertapenem and imipenem) and tigecycline. The isolates which showed reduced susceptibility to carbapenem drugs with reference to CLSI guidelines were confirmed to be carbapenem-resistant by E-test and carba NP test. E-test strip with predefined antibiotic quantitative gradients (ranges 0.002-32 μg/mL) for the corresponding carbapenems like meropenem and imipenem was performed determining its minimum inhibitory concentration (MIC) breakpoints and

its carbapenemase production by Carba NP test.

2.4. E-Test

MIC can be used as a confirmatory test for the detection of carbapenem resistance; this test was performed by E-Test, a quantitative determination of susceptibility of bacteria to antibacterial agents.[11] The overnight bacterial culture was inoculated onto the peptone water and compared with that of 0.5 Mc Farland standards. With the help of sterile cotton swab, a lawn was made on the entire surface of the MHA plate and left for 10 to 15 minutes. The MIC determination strip (Ezy MIC^{TM,} Himedia) of imipenem and meropenem was placed on the surface of the culture lawn and incubated at 37°C for overnight. The result was interpreted according to the CLSI guideline (Figure 1). The CLSI breakpoints are ≤1 μg/ml for imipenem-susceptible, ≥4 μg/ml for imipenem-resistant and ≤1 μg/ml for meropenem-susceptible, ≥4 μg/ml for meropenem-resistant.[12]

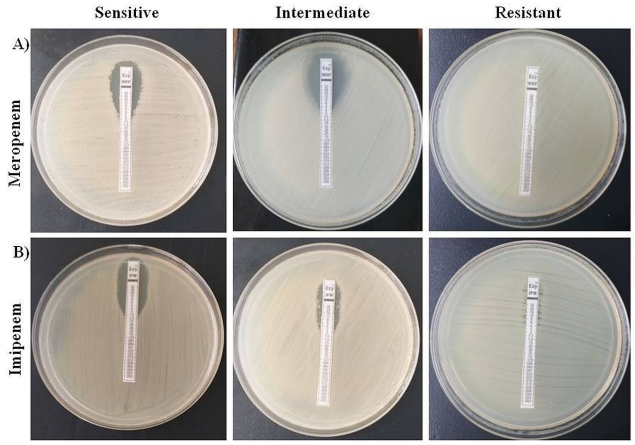

Fig. 1: Performance of E-test to determine the MIC of the 50 CROs. **A**) MHA plates showing quantitative gradient of antibiotic meropenem; **B**) MHA plates showing quantitative gradient of antibiotic imipenem. Categorized as sensitive (≤1), intermediate (=2) and resistance (≥4) for the selected 50 CROs that are resistant against imipenem, meropenem and ertapenem by disc diffusion method

2.5. Carba NP test

A phenotypic method that is used to detect the carbapenemase-producing organisms is carba NP test.

Solution A: 100 μl made up of 0.5% phenol red (Himedia, India) solution and 10mM/L $ZnSO_4.H_2O$ (Himedia, India) at pH 7.8 ± 1.

Solution B: 100 μl made up of 6 mg/ml of imipenem monohydrate (Sigma – Aldrich, USA) and Solution A at pH 7.8 ± 1.

Two-microcentrifuge tubes containing 100 μl of bacterial lysis buffer [20mM/L Tris-HCL (Himedia, India) and 0.1% Triton X-100 (Sigma – Aldrich, USA)] were labelled as "a" and "b". In which, a loop of bacterial colony from blood agar plate were suspended and vortexed for 5 seconds.[7] To which, solution A and B was added to the tube "a" and tube "b", respectively, and incubated at 37°C for up-to 2 hours. The test results were interpreted as positive when the tube "a" was red and tube "b" was orange/yellow and interpreted as negative when both the tubes remain red (Figure 2). Any colour change in tube "a" was considered as invalid result.[12]

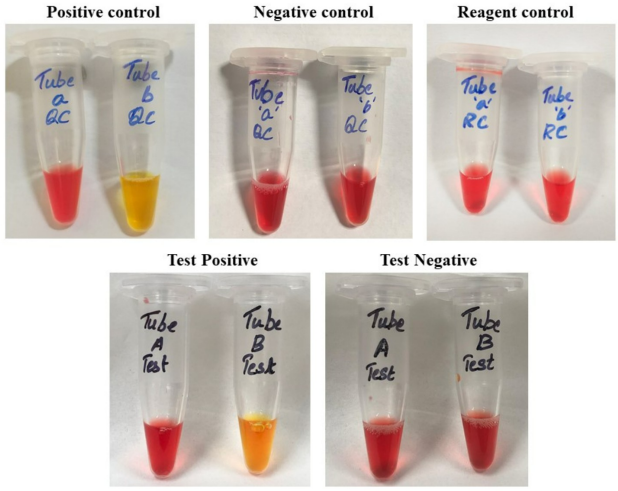

Fig. 2: Performance of Carba NP Test for the production of carbapenemase. Tube 'a' contains solution A (0.5% phenol red solution and 10 mM/L $ZnSO_4.H_2O$) and tube 'b' contains solution B (6 mg/ml of imipenem monohydrate and Solution A). **Positive control** - Klebsiella pneumoniae ATCC BAA-1705; **Negative Control** - Klebsiella pneumoniae ATCC BAA-1706; **Reagent Control** – Uninoculated reagents; **Test positive -** shows the production of carbapenemase enzyme by hydrolysing imipenem, which turns yellow due to a change in pH. **Test Negative** – shows the absence of carbapenemase production and no apparent change in the pH

3. Results

3.1. Isolation and identification of carbapenem resistant organisms (CRO)

In the present study, 716 postoperative clinical samples (Table 1) from 560 males and 156 females were processed for presence of pathogens. Of which, 257 samples were tested positive for microorganisms (323 isolates) that included both gram-positive and gram-negative bacteria (Figure 3). On further classification of the 323 isolates, 230 belonged to be gram-negative bacilli (Figure 4), of which 93 isolates were found to be resistant to carbapenem drugs namely imipenem, ertapenem and meropenem. Of the ninety-three isolates, 50 isolates were collected from

clinical samples of 47 patients (39 males and 8 females) who had undergone various surgical procedures related to the gastrointestinal tract. The patients were between 33 and 65 years of age with the mean age being 46.6 years. The 50 isolates included *Klebsiella species, Escherichia coli,* NFGNB and *Enterobacter species* were further tested via E-Test and Carba NP test. The most common organisms identified in the 50 isolates belonged to *Klebsiella* species (34, 68%) followed by *Escherichia coli* (11, 22%), NFGNB (3, 6%) and *Enterobacter* species (2, 4%). The bacterial isolates obtained from various samples are given in Table 2.

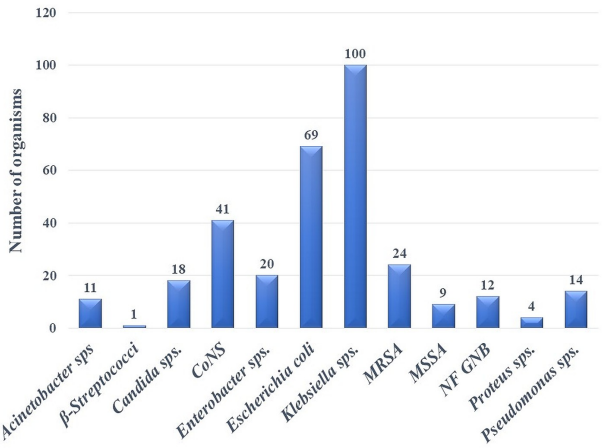

Fig. 3: Isolates found in the gastrointestinal postoperative clinical samples. Clinical samples were processed employing microbiological and biochemical tests. This identified 323 isolates that include both gram-positive and gram-negative organisms. The most commonly found organisms are *Klebsiella* sp (n=100) followed by *Escherichia coli* (n=69) and the least found organism is β-*Streptococci* (n=1). CoNS – Coagulase Negative *Staphylococci*; MRSA – Methycillin-Resistant *Staphylococcus aureus*; MSSA - Methycillin-Sensitive *Staphylococcus aureus*; NFGNB – Nonfermenting Gram-Negative Bacilli

3.2. E-Test

The isolates that showed resistance to carbapenem drugs (imipenem, meropenem and ertapenem) were further subjected to E-test for accessing the MIC of meropenem and imipenem. As per the breakpoint of CLSI guidelines, out of 50 isolates, 47 isolates showed resistance against meropenem (≥4 μg/ml) and 40 isolates showed resistance against imipenem (≥4 μg/ml). These isolates were further classified as Sensitive (S), Intermediate (I) and Resistant (R) based on the stipulated CLSI guidelines respectively (Table 3).

3.3. Carba NP test

The carba NP test differentiates the strains that are carbapenemase-producers from the organisms that show

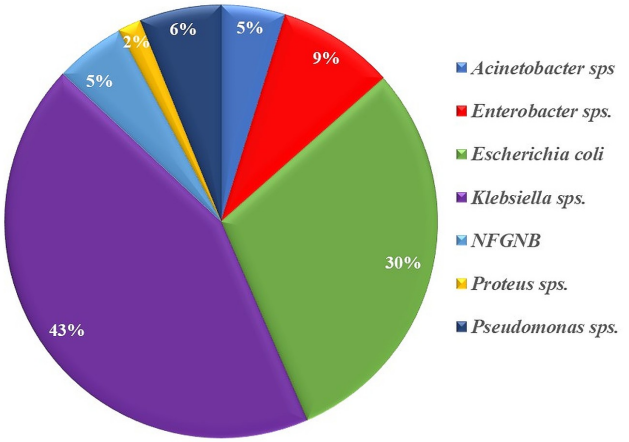

Fig. 4: Pie-chart shows the presence of various gram-negative bacilli organisms. The graph shows percent occurrences of gram-negative bacilli from the previously identified 323 organisms.

carbapenem resistance due to non–carbapenemase mediated mechanisms. Out of 50 isolates tested, 35 isolates were positive for carbapenemase production and 15 isolates were negative (Table 4). The majority of carbapenemase positive organisms were found to be *Klebsiella* species (n=24)followed by *Escherichia coli* (n=7), NFGNB (n=3) and *Enterobacter* species (n=1). These carbapenemase positive isolates were majorly isolated from the clinical specimens such as wound pus, bile, sputum, catheterized tip and blood (Table 5). Of note, the incidence of postoperative *Klebsiella* species infection is higher after most surgical procedures of the gastrointestinal complications (Table 6).

4. Discussion

There is an increase in the incidence of Carbapenem Resistant Organisms (CROs) in postoperative patients in the recent years as a result of prior hospital stay, surgical procedures. This increase may also be associated with prior exposure to the 3^{rd} or 4^{th} generation cephalosporins and carbapenems.[7,13] In our study, 50 isolates from 47 clinical samples were found to be resistant to carbapenem. Of which, 35 isolates were detected to encode for carbapenemase. The most common pathogens found in the isolates tested were *Klebsiella* species (34 of 50; 68%) and *Escherichia coli* (11 of 50; 22%). This result is similar to previous studies where 65.5% and 67.7% of *Klebsiella pneumoniae* encoding carbapenemase were detected from 94 and 124 patients with CRE infection.[13,14] However, in our study the frequency of presence of CROs was higher (40% of 230 gram-negative bacilli isolated) when compared to other reported studies: 30% CRE among 160 isolates and 6% CRE among 100 *Enterobacteriaceae*.[8,15] These differences in the frequencies of occurrence of CROs may arise due to differences in the types of clinical samples

Table 1: Distribution of clinical samples for microbiological screening

S.No.	Samples	Males		Females		Total
		Positive	Negative	Positive	Negative	
1.	Pus/wound pus	52	10	13	1	76
2.	Body fluid	30	92	7	18	147
3.	Urine	18	79	10	27	134
4.	Catheterized tip	31	15	8	5	59
5.	Blood	25	111	8	36	180
6.	Bile	8	8	10	2	28
7.	Sputum	8	3	0	3	14
8.	Throat swab	1	33	0	5	39
9.	Nasal swab	26	10	2	1	39
Total		199	361	58	98	716

Table 2: Distribution of 50 randomly selected isolates from various clinical samples

S.No	Sources	Number of Isolates				Total
		Klebsiella species	Escherichia coli	NFGNB	Enterobacter species	
1.	Wound pus	10	7	-	1	18
2.	Bile	7	2	-	-	9
3.	Catheterized tip	3	1	2	-	6
4	Stent	2	1	-	-	3
5	Sputum	5	-	1	-	6
6	Body fluid	5	-	-	1	6
7	Blood	2	-	-	-	2
Total		34	11	3	2	50

Table 3: Distribution of the 50 CROs based on E-Test

S.No	Isolates	Meropenem			Total	Imipenem			Total
		S ≤1	I 2	R ≥4		S ≤1	I 2	R ≥4	
1.	*Klebsiella* species	1	-	33	34	-	7	27	34
2.	*Escherichia coli*	-	2	9	11	1	-	10	11
3.	NF GNB	-	-	3	3	-	1	2	3
4.	*Enterobacter* species	-	-	2	2	-	1	1	2
Total		1	2	47	50	1	9	40	50

S – Sensitive; I – Intermediate; R – Resistant

Table 4: Carbapenemase detection by carba NP test among the 50 CROs

S.No	Isolates	Carba NP		
		Positive	Negative	Total
1.	*Klebsiella* species	24	10	34
2.	*Escherichia coli*	7	4	11
3.	NF GNB	3	-	3
4.	*Enterobacter* species	1	1	2
Total		35	15	50

Table 5: Clinical sources of carbapenemase producing CROs

S.No	Type of Samples	Isolates				Total
		Klebsiella species	*Escherichia coli*	NFGNB	*Enterobacter species*	
1.	Pus/wound	6	4	-	1	11
2.	Bile	7	2	-	-	9
3.	Sputum	3	-	1	-	4
4.	Body fluid	3	-	-	-	3
5.	Tip	3	1	2	-	6
6.	Blood	2	0	-	-	2
Total		24	7	3	1	35

Table 6: List of surgical procedures and the Carbapenemase-producing CROs

S.No	Clinical Procedures	Carbapenemase Producing Isolates			
		Klebsiella species	*Escherichia coli*	NFGNB	*Enterobacter species*
1.	Cervical Esophagotomy	-	1	1	
2.	Central Hepatectomy	1	-		
3.	Coloplasty			1	
4.	Cholecystectomy	2	1		
5.	Cystojejunostomy	1	1		
6.	Excision of Bile Duct with Cholecystectomy	2			
7.	Hartmann's Procedure Splenectomy	1			1
8.	Laparotomy	3			
9.	Lateral Pancreaticojejunostomy with Perihepatic Pseudocyst Drooping Drainage + Nasojejunal Tube	1			
10.	Longitudinal Pancreatic Jejunostomy	1			
11.	Necrosectomy +Feeding Jejunostomy & Diversion Loop Ileostomy	2			
12.	Open Cholecystectomy	3	2		
13.	Percutaneous Transhepatic Biliary Drainage	1			
14.	Total Gastrectomy	1			
15.	Transperitoneal Nephrectomy + Loop Ileostomy	2		1	
16.	Whipple's Procedure	3	2		

analysed and the environment of the study. Thus, one likely possibility for the higher incidence of CROs in our study may be due to the analysis of samples from a tertiary care Hospital where surgical procedures are routinely performed.

In order to further analyse the antibiotic resistance capabilities of the 50 selected isolates, we performed the E-test to determine the MIC of the antibiotics. Here, we chose to test for only imipenem and meropenem (among the three common carbapenem drugs) because many studies have revealed that the mechanism of resistance to ertapenem (another carbapenem drug) is most often mediated by non-carbapenemase mechanisms. [16,17] Among the 50 CROs tested, only 47 (94%) and 40 (80%) isolates showed resistance in the E-test for meropenem and imipenem respectively. A lack of a 100% resistance outcome in the E-tests may be because of differences in their resistance mechanisms in the remaining non-confirming isolates. Such differences in the resistance outcome of the CRO strains to E-tests Vs disc diffusion test have been previously reported as well for e.g., in one study only two strains were positive in an antimicrobial gradient test among 43 strains of CRE. [16,18–20] Nevertheless, no such discordance between the E-test and disc diffusion test for carbapenems has also been reported. [8] Overall, the use of E-test does help in further isolating specific antibiotic resistant organisms of the CRO class.

Among the 50 CRO isolates, 6 isolates of *Klebsiella* species showed intermediate susceptibility against imipenem while resistant to meropenem (Table 3). Recently, it has been shown that a strain is resistant against almost all β-lactams including meropenem but is susceptible to imipenem — in 2012, in Japan 5 isolates of ISMRK (imipenem–susceptible but meropenem–resistant *Klebsiella*) was found on surveillance of ESBL producing *Escherichia coli* and *Klebsiella pneumoniae* from 17 general Hospitals in Hiroshima. These 5 isolates showed MIC range against meropenem between 32 μg/ml and 64 μg/ml and against imipenem at 1 μg/ml by a broth micro dilution method and by a microscan system respectively. Mapping their genome showed the presence of bla$_{IMP-6}$ and bla$_{CTX-M-2}$ genes, which could contribute to their ISMR characteristic.[21] Similarly, in 2014, in Mumbai, a study reported an ISMR isolate of *K. pneumoniae* MS5166 from a urine sample, which showed resistance to almost all β-lactam antibiotics, but was susceptible to imipenem as per CLSI criteria.[22] Thus, the discordance in the antibiotic susceptibility between imipenem and meropenem in our 6 isolates of *Klebsiella* species may also be indicative of ISMRK.

In general, the mechanism of carbapenem resistance in CROs is often mediated by the production of carbapenemase. Carbapenemases are β-lactamases, the production of the carbapenem hydrolysing beta-lactamases confer resistance to almost all β-lactams.[23] It has been widely acknowledged that carbapenemase-producing CROs cause a higher rate of mortality. In addition, horizontal transfer of carbapenemase gene(s) has also been implicated in the spread of transferable resistance.[24,25] Therefore, speedy identification of the carbapenemase producing organisms in a clinical set up will enable better treatment options. A novel, short-duration, phenotypic method for the detection of carbapenemase producing gram negative bacilli is the carba NP test.[5,23] In our study, we employed the carba NP test for the 50 CROs and identified that only 35 (70%) were positive for carbapenemase production. This is comparable to other reported studies i.e, 57.5%, 76.3% and 80.6% strains were positive for carbapenemase production among 120, 76 and 144 CRE strains.[8,26,27] The remaining (approximately 30%) of the isolates that were negative for carbapenemase production did show carbapenem drug resistance in disc diffusion test. This may be due to differences in their mechanism(s) of resistance: loss of porin channels, hyper-production of AmpC β-lactamases or ESBL or overexpression of efflux pumps.[28]

5. Conclusion

CROs spread rapidly and cause therapeutic challenges in treatment as carbapenem drug is administered as the last line of treatment. Hence it is recommended that the antibiotic-susceptibility pattern-guided therapy should be followed. The resistance of these bacteria is primarily ascribed by the production of carbapenemase enzyme. Hence, a novel, short-duration, phenotypic method (carba NP), performed directly from the colonies grown on culture plates will be helpful in detecting patients infected with carbapenemase producers even before the performance of antimicrobial susceptibility test. Thus, the early detection of carbapenemase activity may limit the spread of infections in the health care settings. Moreover, performing a carba NP test may even help to decrease the time to detect the carbapenemase producing CROs by at least 24 hours in the clinical setting.

6. Source of Funding

None.

7. Conflict of Interest

The authors declare no conflict of interest.

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