



Global priority critical pathogens-its prevalence and molecular epidemiology in Arar tertiary care hospital, Saudi Arabia

Prevalence of global priority critical pathogens

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Abstract

Aim: The aim of this study is to identify the global priority critical pathogens from various clinical specimens and confirming the presence of enzymes which are responsible for their resistance using Carba NP test and molecular methods. **Material and Method:** It is a prospective hospital-based study, performed during a period of one year. Data were collected from samples which were sent to the microbiology laboratory at Arar Central Hospital. All samples were screened for the presence of global priority critical pathogens using standard bacteriological techniques and all isolates were subjected for antibiotic sensitivity testing to detect the presence of Carbapenem Non-Susceptible Organisms. Further testing was performed to detect the presence of carbapenem-hydrolyzing enzymes among the resistant strains by Rapidec Carba NP test and the presence of the resistance gene was detected by Xpert Carba-R Assay. **Results:** Out of 926 Gram-negative bacteria, 64 (6.9%) were carbapenem non-susceptible organisms (CNSOs). The minimum inhibitory concentration (MIC) for ertapenem and meropenem was $>4 \mu\text{g/mL}$ and $>8 \mu\text{g/mL}$ respectively for all CNSOs. Rapidec Carba NP test was positive for 98% of CNSOs, and Xpert Carba-R assay detected the presence of carbapenemase gene in 43.7% of CNSOs. **Discussion:** An increase in the prevalence of carbapenem-resistant organisms from the clinical isolates highlights the importance of active surveillance which will help in the implementation of antibiotic stewardship and infection control measures in the hospitals, and in achieving the global action plan on antibiotic resistance.

Keywords

Global Priority Critical Pathogens; Carbapenemase-Producing Enterobacteriaceae; Gram-Negative Bacilli; Carba NP Test; Carbapenem Non-Susceptible Organisms; Xpert Carba-R; Arar

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Introduction

In 2017, the World Health Organization (WHO) has drawn up a list of the drug-resistant bacteria that pose the biggest threat to human health. The list of organisms is known as global priority pathogens. The global priority critical pathogens are Carbapenem-resistant Enterobacteriaceae, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*; and 3rd generation cephalosporin-resistant Enterobacteriaceae [1].

Carbapenems are the last option for treating infections due to the Gram-negative bacilli (GNB), including those producing extended-spectrum β -lactamases (ESBL). Resistance to carbapenems by the Gram-negative bacilli remains a problem in treating infections as the treatment options are very limited and complicated [2]. Moreover, the global spread of these Carbapenem non-susceptible organisms (CNSOs) species is a critical medical and public health issue worldwide in terms of morbidity, mortality and economic cost [3].

Resistance to carbapenems in Gram-negative bacilli are either due to a combination of structural mutations leading to decreased outer-membrane permeability and production of other β -lactamase enzymes or by the production of carbapenemases [4]. Carbapenemase production can be either chromosomal or plasmid-based. Being highly transferable, plasmid-mediated carbapenem resistance is responsible for outbreaks and they are largely associated with multi- and pan-drug resistance [5]. According to the molecular structural classifications, carbapenemases belong to one of the three groups of β -lactamases namely Ambler class A, B, and D groups. Class A and D carbapenemases require serine at their active site (serine carbapenemases) and it includes chromosomally as well as plasmid-encoded carbapenemases, whereas Class B, the Metallo- β -lactamases (MBLs), are zinc-dependent. *K. pneumoniae* carbapenemase (KPC), IMI, SME, GES, and NMC-A belongs to Class A carbapenemases; Class B carbapenemases includes IMP, VIM and NDM β -lactamases; and Class D carbapenemases oxacillinase OXA-48 derivatives [4, 6].

Such detailed information on the CNSOs as its prevalence and periodic epidemiological investigation of the resistance gene will be helpful in the implementation of antimicrobial stewardship plans at a national level. Hence, the study concentrated on the prevalence of global priority critical pathogens (especially carbapenem-resistant Enterobacteriaceae (CRE), carbapenem-resistant *Pseudomonas aeruginosa*, and carbapenem-resistant *Acinetobacter baumannii*) from various clinical specimens and confirming the enzymes responsible for their resistance using molecular methods.

Material and Method

This prospective study was performed in the Department of Microbiology between August 2017 and July 2018. The study was approved by the Institutional Review Board (IRB) and the Committee for Biological and Medical Ethics. All samples received for bacterial culture was included in this study. Data were collected from various samples sent to the microbiology laboratory. Samples were processed according to the standard microbiological technique to identify the organisms [7, 8]. All Gram-negative bacilli and Gram-negative coccobacilli isolates were subjected for the in-vitro antibiotic-susceptibility test using the Kirby-Bauer disk diffusion method as described by Clinical and Laboratory Standards Institute guidelines (CLSI-2017). Organisms which were resistant to imipenem (10 μ g), meropenem (10 μ g) and ertapenem (10 μ g) are designated as suspected

carbapenemase-producing organisms. The antibiotic disks for Kirby-Bauer disk diffusion method were purchased from Oxoid and Bio-Rad Company and quality control was done using *E.coli* ATCC 25922. Ertapenem non-susceptibility is the sensitive marker for carbapenemase-producing Enterobacteriaceae; as it has the ability to detect low-level carbapenemase producers [3]. Minimal inhibitory concentration (MICs) for imipenem, meropenem, and ertapenem were determined by Siemens Microscan WalkAway 40SI to confirm the reduced susceptibility to carbapenem in the isolated organism. The MIC of >4 μ g/mL for imipenem and meropenem or the MIC of >2 μ g/mL for Ertapenem is considered as suspected carbapenemase-producing organisms among Enterobacteriaceae. *Acinetobacter baumannii* and *Pseudomonas aeruginosa* with MIC of >8 μ g/mL for imipenem and meropenem were considered as suspected carbapenemase-producing organisms (CLSI-2017).

These suspected carbapenemase-producing organisms were further tested by Rapidec Carba NP test for phenotypic confirmation and Xpert Carba-R Assay to confirm the presence of enzymes.

Rapidec Carba NP test

The Rapidec Carba NP test (bioMérieux) was performed as recommended by the manufacturer. The test was performed to the strains that were grown on Mueller Hinton E agar plates (bioMérieux). A calibrated 10- μ l loopful of the bacterial colony was picked from the agar plates and mixed into the API suspension medium to get a uniform turbidity equivalent to the standard given in the kit. The bacterial suspension was then transferred to the wells in the test strip and incubated at 37°C for 30 to 40 minutes. A visual reading of the strip was done after 30 minutes by placing the strip on the two-colored (black and white) support. The strip was reincubated further if the test was negative, and the final reading was done after 2 hours. The test well was compared with the control well and a positive test is indicated by a color change from red to yellow; whereas the negative test was indicated by red color as shown in Figure 1. *Klebsiella pneumoniae* ATCC BAA-1705 and *Klebsiella pneumoniae* ATCC BAA-1706 were used as positive and negative controls.

Xpert Carba-R Assay

The Xpert Carba-R Assay is a real-time polymerase chain reaction assay for rapid detection of carbapenemase gene in the carbapenem non-susceptible organisms. It can be able to detect five carbapenem resistance genes like *blaKPC*, *blaVIM*, *blaOXA-48*, *blaIMP-1* and *blaNDM*. The suspected carbapenemase-producing organisms were inoculated on nutrient agar plates and incubated at 35 °C for 18–24 hours in ambient air. Direct colony suspension method was used to prepare a saline suspension, equivalent to 0.5 McFarland standards [9]. Using a 10- μ l loop, the saline suspension was transferred to a 5mL vial the sample reagent. The sample-reagent vial was capped tightly and vortexed at a high speed for 10 seconds. Approximately 1.7 ml of suspension from the sample-reagent vial containing a sample was transferred to the sample chamber large opening of the Xpert Carba-R Assay cartridge and after closing the cartridge lid it was placed into the GeneXpert instrument. The test results were interpreted according to the fluorescent signals displayed in the result window by the Cepheid GeneXpert System.

Results

A total of 926 Gram-negative bacteria were isolated from 3993 clinical specimens. These specimens were collected from various intensive care units (ICU), wards and outpatient departments for a period of one year. Out of 926 Gram-negative bacteria, 64 (6.9% 64/926) were carbapenem non-susceptible organisms (CNSOs). The distribution of CNSOs isolated from various specimens is shown in Table 1. Other Gram-negative bacteria that were sensitive to carbapenem were not included in Table 1.

Table 1. Distribution of carbapenem non-susceptible organisms (CNSOs) isolated from various specimens

Study isolates (n)	Specimens					Total CNSOs
	BAL*	Pus/ Wound swab	Blood	Urine	Sputum	
<i>Acinetobacter baumannii</i> (102)	16	4	5	3	11	39
<i>Klebsiella pneumoniae</i> (172)	10	3	4	1	1	19
<i>Pseudomonas aeruginosa</i> (57)	-	2	-	-	1	3
<i>Klebsiella oxytoca</i> (23)	-	2	-	-	-	2
<i>Enterobacter cloacae</i> (4)	-	1	-	-	-	1
Total (358)	26	12	9	4	13	64

BAL* - Bronchoalveolar lavage

CNSOs - Carbapenem non-susceptible organisms

The minimum inhibitory concentration (MIC) for ertapenem was >4 µg/mL, and for imipenem and meropenem it was >8 µg/mL for all CNSOs. The Rapidec Carba NP test was positive (98%) for all the CNSOs except one *Acinetobacter baumannii*. Rapidec Carba NP test results are shown in Figure 1.

The Xpert Carba-R assay detected the presence of carbapenemase gene in 19 isolates of *Klebsiella pneumoniae*, of which 16 (84.2%) were positive for *bla*_{OXA-48}, two isolates (10.5%) of *Klebsiella pneumoniae* had *bla*_{NDM} and one isolate (5.2%) expressed a dual carbapenemase gene (*bla*_{NDM} and *bla*_{OXA-48}). Three isolates of *Klebsiella oxytoca* had OXA-48 and one *Enterobacter cloacae* expressed VIM gene. Three isolates of *Pseudomonas aeruginosa* (100%) and two from *Acinetobacter baumannii* (5.1%) were positive for *bla*_{VIM}. Distribution of carbapenemase gene in the CNSOs with respect to specimens is shown in Table 2.

Table 2. Specimen wise distribution of carbapenemase gene in the carbapenem non-susceptible organisms (CNSOs).

CNSOs-Study isolates(n)	Carbapenemase gene							Total number of CNSOs with gene
	<i>bla</i> _{OXA-48}	<i>bla</i> _{NDM}	<i>bla</i> _{IMP-1}	<i>bla</i> _{VIM}	<i>bla</i> _{KPC}	<i>bla</i> _{NDM+}	<i>bla</i> _{OXA}	
<i>Klebsiella pneumoniae</i> (19)	BAL -9 Pus -3 Blood -3 Urine -1	BAL -1 Blood -1	-	-	-	-	Sputum -1	19
<i>Klebsiella oxytoca</i> (3)	Pus -3	-	-	-	-	-	-	3
<i>Enterobacter cloacae</i> (1)	-	-	-	Pus -1	-	-	-	1
<i>Pseudomonas aeruginosa</i> (3)	-	-	-	Pus -2 Sputum -1	-	-	-	3
<i>Acinetobacter baumannii</i> (39)	-	-	-	BAL -2	-	-	-	2

BAL* - Bronchoalveolar lavage

CNSOs - Carbapenem non-susceptible organisms

Discussion

In a review about antimicrobial resistance, it has been estimated that the death toll may raise around 10 million deaths per year worldwide because of antibiotic resistance by 2050. The burden of antimicrobial resistance is escalating day by day and it remains a major concern for the global economy [10]. Acknowledging the magnitude of the burden, on 27 February 2017, the WHO has released a list of 'global priority pathogens' (GPP). This list consists of 12 species of bacteria which were grouped under three categories namely; critical (Carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae*; 3rd generation cephalosporin-resistant *Enterobacteriaceae*), high (six species) and medium (three species). This list was intended to help in prioritizing the research and development (R&D) of new and effective antibiotic treatments [1].

The critical group consists of carbapenem-resistant *Enterobacteriaceae* (CRE), *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, and 3rd generation cephalosporin-resistant *Enterobacteriaceae*. These global critical priority pathogens pose threat in health-care settings, nursing homes, and in patients who require a ventilator and venous/arterial catheter (WHO-2017) which could lead to life-threatening bloodstream infections and pneumonia. In order to have more reliable estimates on antimicrobial-resistance burden, the important prerequisite is to have periodic and comprehensive antimicrobial resistance surveillance data [10].

In our study, out of 926 Gram-negative bacteria, 64 (6.9%) isolates were found to be CNSOs. Our study included all Gram-negative bacteria and so the prevalence was 6.9%. The prevalence may be high or different if only the multi-drug resistant Gram-negative bacilli (GNB) were included. In Saudi Arabia, the bacterial resistance among the gram-negative organisms is increasing including the prevalence rate of carbapenem-resistant GNB [11, 12].

Out of 102 isolates of *Acinetobacter baumannii*, 39 were carbapenem-resistant (38.2%) in our study. In Saudi Arabia, reports from various studies conducted between 2009 and 2010 showed that the resistant percentage rate varied from 5.4% to 90.5%, which clearly indicates the increasing nature of resistant pattern in this nosocomial pathogen [13, 14]. A recent study indicated that the susceptibility of *Acinetobacter baumannii* to carbapenems is much reduced to 0.05% and 0.04% to imipenem and meropenem respectively [15]. Our study detected 11% (19/172) of carbapenem-resistant *Klebsiella pneumoniae*. Much higher percentage of carbapenem-resistant *Klebsiella pneumoniae* was reported (52%) in a study conducted in a tertiary and academic hospital in Riyadh [16]. The prevalence of

carbapenem-resistant *Klebsiella oxytoca* and *Enterobacter cloacae* were 8.7% (2/23) and 25% (1/4) respectively in our study and no other organism in family *Enterobacteriaceae* was found to be resistant to carbapenem group of drugs in our study period.

The Rapidec Carba NP test was positive (98 %) for all the CNSOs isolates except one *Acinetobacter baumannii*. The Carba NP test is a recommended phenotypic confirmatory test by Clinical and Laboratory Standards Institute guidelines (CLSI-2015) for the detection of carbapenemase in CNSOs. When compared with molecular-based techniques Carba NP test was 100% sensitive and specific for *Enterobacteriaceae* [17]; and in another study, it was reported that the test is 100% sensitive and 94.4% specific for carbapenemase-producing *Pseudomonas* spp. [18]. In concordance with these statements, our study detected the presence of carbapenemase in all the 22 isolates of Carbapenem-resistant *Enterobacteriaceae* which included 19 isolates of *Klebsiella pneumoniae*, *Klebsiella oxytoca* (2) and *Enterobacter cloacae* (1). As for the non-fermenting gram-negative bacteria concerned, three carbapenem-resistant *Pseudomonas aeruginosa* was isolated and all were positive for carbapenemase by Rapidec Carba NP test; whereas out of 39 carbapenem-resistant *Acinetobacter baumannii*, 38 isolates (97%) showed carbapenemase activity by Rapidec Carba NP test. One of the limitations of the test is some OXA-type carbapenemase-producing *Acinetobacter baumannii* strains may not be detected by Rapidec Carba NP.

Out of 64 CNSOs, Xpert Carba-R assay detected carbapenem gene in 28 isolates (43.7%). Among the 19 isolates of *Klebsiella pneumoniae*, OXA-48 was the predominant carbapenemase gene (16, 84%) followed by two isolates with NDM (10%) and one isolate (5%) expressed dual carbapenemase gene (NDM and OXA-48). The observation is similar to other studies in Saudi Arabia with respect to *Klebsiella pneumoniae* [16,19,20]. Three isolates of *Klebsiella oxytoca* had OXA-48 and one *Enterobacter cloacae* expressed VIM gene. All the three isolates of *Pseudomonas aeruginosa* (100%) which were resistant to carbapenems had VIM gene. These results were in concordance with the other studies which reported VIM as the common gene among *Pseudomonas aeruginosa* [21]; except one study which was done in Makkah hospitals that reported 22.6% of IMP gene [22].

In this study, we found only 5.1% (2/39) of *Acinetobacter baumannii* were positive for the VIM carbapenemase gene; another 37 strains (94.8%) are negative for another carbapenemase gene like *bla_{KPC}*, *blaOXA-48*, *blaIMP-1* or *blaNDM*. In contrast to our observation, other local studies reported the presence of OXA-23, OXA-51, and OXA-40 as their predominant carbapenemase gene in *A. baumannii* [22-24]. As Xpert Carba-R assay detects only the presence of OXA-48, VIM, NDM, KPC, and IMP-1; the presence of another gene can be missed in these 37 isolates which were positive by the Rapidec Carba NP test. One of the limitations in Xpert Carba-R assay is that the mutations or polymorphisms in primer or probe binding regions may affect the detection of new or unknown variants of a gene resulting in a false negative result. However, the resistance to carbapenems in *Acinetobacter baumannii* is not only because of carbapenem-hydrolyzing class D β -lactamases but also due to other mechanisms like porins modifications (channel for the influx of carbapenems) or penicillin-binding protein modifications [25]. In 2015, multicenter study conducted in Saudi Arabia reported eight carbapenem-resistant isolates in the Arar region. It comprises three OXA-51 like, two oxa-23 like and one oxa-72 in

Acinetobacter baumannii; *Enterobacter cloacae* and *Pseudomonas aeruginosa* one each having VIM-4 and VIM-2 respectively [3]. We observed 64 CNSOs, of which 28 had various carbapenemase genes in Arar region. This indicates that there is a considerable increase in the prevalence of CNSOs in this region and in another region of Saudi Arabia. It is highly recommended to have detailed information on the antimicrobial resistance prevalence and regional wise epidemiological investigation about the resistance gene which will help in the implementation of antibiotic stewardships at the national level [26]. It is also suggested to have rapid detection of carbapenemase gene by Xpert Carba-R assay in CNSOs which might help the clinicians to decide on antibiotic therapy and for infection control measures to avoid outbreaks [27].

Moreover, one of the five objectives of global action plans on antimicrobial resistance is to strengthen the knowledge through surveillance and research (WHO-2015). These findings suggest periodic surveillance of carbapenem-resistant organisms in hospitals and rapid detection of carbapenemase gene favors not only in antibiotic stewardship but also in the implementation of infection control measures.

Limitation

Our study identified *Acinetobacter baumannii* organisms which were negative by Xpert Carba-R assay but positive in Rapidec Carba NP test. All these isolates are stored to perform multiplex PCR to rule out the absence of carbapenemase gene in the near future.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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