

**Original Article**

## **Study on Incidence of Carbapenem Resistant Nonfermenting Gram Negative Bacilli from patients with Respiratory Tract Infections among Intensive Care Units.**

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### **Abstract:**

**Introduction:** Nonfermenting gram negative bacilli like are known to produce serious lower respiratory infections in ICU patients.

**Materials and Method:** 200 respiratory specimens were collected from patients admitted in ICU. Organisms were identified by standard procedures and antibiotic sensitivity was performed by using disk diffusion methods.

**Results:** *Pseudomonas aeruginosa* and *Acinetobacter spp* were the predominant non fermentative gram negative bacilli isolated and shown multidrug resistance.

**Conclusion:** The non fermentative gram negative bacilli like *Pseudomonas aeruginosa* and *Acinetobacter spp* showed carbapenam resistance and judicious use of antibiotics are warranted to control infections produced by them.

**Key words:** Non fermentative gram negative bacilli, carbapenam resistance, *Pseudomonas aeruginosa*, *Acinetobacter spp*. Kirby Bauers disk diffusion method.

### **Introduction:**

Nonfermenting gram-negative bacilli (NFGNB) are a taxonomically diverse group of aerobic, nonsporing, bacilli that either do not utilize glucose as a source of energy or utilize it oxidatively.<sup>[1]</sup> They occur as saprophytes in the environment and some are also found as commensals in the human gut.<sup>[2],[3]</sup> They cause serious infections in immunocompromised and hospitalized patients especially those admitted to intensive care units (ICU).<sup>[4]</sup>

Lower respiratory tract infections are the most common bacterial infections among patients in intensive care units occurring in 10-25% of all ICU patients and resulting in high overall mortality, which may range from 22-71%.<sup>[5,6]</sup>

Most common bacterial agents of LRTI in the ICU are *Pseudomonas*, *Acinetobacter*, *Klebsiella*, *Citrobacter*, and *Escherichia coli*.<sup>[7,8,9]</sup> These organisms further worsen the situation by virtue of their multi drug resistance and thus limit therapeutic options.<sup>[4]</sup>

In almost all cases, there is a need to initiate empirical antimicrobial treatment before obtaining the microbial results, but the situation is further complicated by the emergence of multiple  $\beta$ -lactamase producers and multi drug resistant pathogens.<sup>[10]</sup>

Carbapenems were first introduced in 1980.<sup>[11, 12, 13]</sup> Four carbapenems Imipenem, Meropenem, Ertapenem and Doripenem are currently approved for use<sup>[14]</sup> and are now frequently used as the last choice in treating serious infections caused by multidrug resistant gram negative bacilli. These antibiotics are stable to  $\beta$ -lactamases including the extended spectrum  $\beta$ -lactamases (ESBLs) and AmpC produced by gram negative bacilli.<sup>[11, 12, 13]</sup>

Ertapenem is considered a narrower spectrum agent, as it has limited activity against certain pathogens of concern such as *P.aeruginosa*. The other three carbapenems have a broader spectrum of activity. Doripenem is a newer antibiotic with broad spectrum of activity against various gram-positive and gram-negative aerobic and anaerobic bacteria, including many multi-drug resistant gram-negative pathogens. Improved potency against non-fermentative gram-negative bacteria has also been demonstrated with doripenem compared with other carbapenems.<sup>[14]</sup> NFGNB are innately resistant to many antibiotics and are known to produce extended spectrum  $\beta$ -lactamases and metallo  $\beta$ -lactamases.<sup>[3, 15]</sup> *Pseudomonas aeruginosa* and *Acinetobacter species* in particular are most often associated with carbapenem resistance. This is of significance since NFGNB can cause fatal lower respiratory tract infections in patients admitted to ICU.<sup>[16]</sup>

Nosocomial infection is a serious challenge as it increases significantly the morbidity and mortality, besides, the high incidence of gram negative bacteria and development of multi-drug resistance still remains a serious problem. This has fueled the development and addition of newer antibiotics to the armamentarium and many guidelines for their use as well.<sup>[12]</sup> The present study was undertaken to identify the non fermentative gram negative bacilli among the patients admitted at ICU of a tertiary care hospital

#### **Materials and methods:**

A total of 200 samples were collected from patients of all age groups with clinical evidence of lower respiratory tract infections admitted to Medical (MICU), Surgical (SICU), Neuro (NICU), and Pediatric (PICU) wards of Narayana General Hospital, Nellore over a period of one year and the samples were processed with standard procedures. The specimens included sputum and endotracheal aspirates from suction tip. Gram stain was performed for the samples collected and cultured on appropriate media. The nonfermentative organisms were isolated using standard procedures. Antibiotic sensitivity was performed by Kirby Bauers disk diffusion methods using

Ampicillin(10 $\mu$ g), Imipenem(10 $\mu$ g), Meropenem(10 $\mu$ g), Gentamicin(10 $\mu$ g), Cefotaxime(30 $\mu$ g), Ceftazidime(30 $\mu$ g), Cefepime(30 $\mu$ g) and amikacin (30 $\mu$ g) disks.

**Results and Discussion:**

A total of 200 samples were collected; which included 87 sputum (43.5%) and 113 endotracheal aspirates (56.5%). Among the various isolates the gram-negative nonfermentative bacilli like *Pseudomonas aeruginosa* (38) and *Acinetobacter* (50) were isolated. Antimicrobial resistance profiles of *Pseudomonas* isolates by disk-diffusion method (n=38) is given in Table 1.

Table 1:

<u>Antibiotics</u>	<u>Resistant isolates</u>	<u>Percentage</u>
Ampicillin	32	84
Cefotaxime	27	71
Ceftazidime	37	97
Cefpirome	29	76
Gentamicin	27	71
Amikacin	21	55
Imipenem	<b>16</b>	<b>42</b>
Meropenem	<b>11</b>	<b>29</b>

**Antimicrobial resistance profiles of *Acinetobacter* isolates by disk-diffusion method (n=50):**

Table 2

<u>Antibiotics</u>	<u>Resistance</u>	<u>Percentage</u>
Ampicillin	45	90
Cefotaxime	31	62
Ceftazidime	45	90
Cefpirome	45	90
Gentamicin	45	90
Amikacin	36	72
Imipenem	<b>14</b>	<b>28</b>
Meropenem	<b>12</b>	<b>24</b>

**Carbapenam resistance among nonfermenters: Table 3:**

<u>Organism tested</u>	<u>Antibiotic</u>	<u>No of Resistant isolates</u>	<u>Percentage</u>
<i>Pseudomonas aeruginosa</i>	Imipenem	16	42
	Meropenem	11	29
<i>Acinetobacter spp</i>	Imipenem	14	28
	Meropenem	12	24

*Pseudomonas aeruginosa* and *Acinetobacter* spp. in particular are most often associated with carbapenem resistance. This is of significance since NFGNB can cause fatal lower respiratory tract infections in patients admitted to ICU. The present study documents the carbapenem resistance among NFGNB in a total of 200 samples collected from patients admitted in Intensive Care Units with lower respiratory tract infections over a period of one year in Narayana General Hospital, Nellore. Among the 200 samples processed, 168 (84%) were positive for culture and 32 (16%) were negative for culture. Among the total of 200 samples collected, 87 (43.5%) were sputum samples and 113 (56.5%) were Endo Tracheal Aspirates from patients on ventilators

Multidrug-resistant *Acinetobacters* and *Pseudomonas* spp. are common in hospitals, especially in the ICUs. Among all the isolates from total number of samples collected and processed, *Klebsiella* spp. remains at the top of the table with 81 (48.21%) followed by *Acinetobacter* spp. 50 (29.76%), *Pseudomonas* spp. 38 (22.61%), *Streptococcus* spp. 32 (19.04%), *Escherichia coli* 28 (16.66%), *Moraxella* spp. 12 (7.14%), *Proteus* spp. 10 (5.95%), *Citrobacter* spp. 09 (5.35%), *Candida* 09 (5.35%), *Staphylococcus aureus* 07 (4.16%), *Enterobacter* spp. 05 (2.97%), and CONS 05 (2.97%).

More prevalent isolates from ET aspirates were *Acinetobacter* which constitutes 32 (11.19%) and sputum 18 (6.29%) accounting for a total of 50 (17.48%) and *Pseudomonas* with a lower prevalence of 15 (5.24%) from sputum and 23 (8.04%) from ET aspirates accounting for a total of 38 (22.61%). Kirby-Bauer disc diffusion method was performed to 38 *Pseudomonas* isolates, ceftazidime resistance was 97% which was alarmingly high, observations were made by various investigators like Veena Kumari et al.<sup>[17]</sup> and Sofianou et al.<sup>[18]</sup> who reported 96-100% resistance; where as Pfaller MA et al.<sup>[19]</sup> has reported a lower rate of resistance (37-67.5%) to ceftazidime. High rate of resistance at our centre may be due to the selective influence of extensive usage of third generation cephalosporins followed by Ampicillin 84%, Cefpirome 76%, Cefotaxime and Gentamicin 71%, Amikacin 55%, Imipenem 42% and lower resistance to Meropenem 29%.

Multiple factors contribute to make *Pseudomonas aeruginosa* a nosocomial pathogen like injudicious administration of broad-spectrum antibiotics, instrumentation, and intrinsic resistance of microorganisms to numerous antimicrobial agents. The introduction of carbapenems into clinical practice was of great help in the treatment of serious bacterial infections caused by beta-lactam-resistant bacteria. Carbapenems, due to their stability to hydrolysis by most beta-lactamases, have been the drugs of choice for treatment of infections caused by penicillin-resistant or cephalosporin-resistant gram-negative infections.

In 50 *Acinetobacter* isolates, Ceftazidime, Ampicillin, Cefpirome and Gentamicin resistance was 90% which was high followed by Amikacin 72%, Cefotaxime 62%, Imipenem 28% and lower resistance to Meropenem 24%.

It shows a considerably higher prevalence of resistance among *P. aeruginosa* (42.10%) than *Acinetobacter* spp. (28%) to imipenem and *P. aeruginosa* (29.82%) than *Acinetobacter* spp. (24%) to meropenem. Similar data available in the Indian Literature is Gladstone et al.<sup>[20]</sup> in 2005 reported 12.2% carbapenem resistance among NFGNB with higher prevalence in *Pseudomonas* (42.8%) than *Acinetobacter* (14.2%); however, Taneja et al.<sup>[16]</sup> reported that 36.4% of the nonfermenters (n=85) causing nosocomial urinary tract infections were resistant to

imipenem. In another study Navaneeth et al.<sup>[7]</sup> reported a prevalence of 12% carbapenem resistance among 50 strains of *Pseudomonas aeruginosa* isolated from various clinical specimens.

Carbapenem resistance in *Acinetobacter spp.* is an emerging problem and is a cause of concern as many nosocomial *Acinetobacter* are detected to be resistant to most other antibiotics. Several phenotypic and molecular typing methods are used to investigate the origin of infection, route of spread and prevalence of isolates in a bacterial population. Another Indian study by Taneja et al.<sup>[16]</sup> in 2003 reported a high incidence of more than 20% carbapenem resistance among *Acinetobacter*. Corbella and co-workers found carbapenem resistance among the *Acinetobacter spp.* from patients in ICU to be as high as 36%.<sup>[21]</sup> Manikal et al. observed a high rate of 50% carbapenem resistance among *Acinetobacter* in a New York Hospital.<sup>[22]</sup> Oxacillinases are less efficient in hydrolyzing carbapenems than the metalloenzymes but are known to occur commonly in carbapenem-resistant *Acinetobacter*. We found that incidence of resistance against Meropenem was less than Imipenem. Meropenem is well-tolerated and offers several potential advantages, including greater *in vitro* activity against Gram-negative pathogens and the option of bolus administration. In various studies across the world, varying rates of resistance (4-60%) have been reported for imipenem and meropenem.<sup>[8]</sup> There is a high incidence of multidrug-resistant *P.aeruginosa* from patients with type-2 diabetes mellitus.<sup>[23]</sup>

#### **Conclusion:**

Our study documents an increase in the carbapenem resistance. This highlights that unwarranted and unrestricted usage of antibiotics is associated with emergence of resistance in common nosocomial pathogens like *Acinetobacter spp.* A coordinated effort to limit inappropriate use of broad-spectrum antibiotics, efficient hospital antibiotic policies, vigilant detection of resistant *Acinetobacter*, rigorous surveillance and infection-control protocols are needed to control the increasing incidence of highly resistant non fermenting Gram negative bacilli.

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