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Research Article

Antibiotic Sensitivity Pattern of Bacterial Isolates from the Intensive Care Unit of a Tertiary Care Hospital in India

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Abstract

Purpose: *To undertake an audit of the antimicrobial (AM) sensitivity pattern of bacterial isolates in the intensive care units (ICU) of a tertiary hospital of Bhavnagar, India.*
Methods: *Retrospective analysis of the indoor case papers of ICUs from January 2010 to 31st March 2011 was carried out at Department of Pharmacology, Govt. Medical College and Sir Takhtsinhji General Hospital, Bhavnagar, India. Information collected include demographic data of the patient, admission unit, duration of hospital stay, diagnosis, type of infection, empirical treatment, indication of the use of the antimicrobials (AMs). Others include collected specimen, causative agent, sensitivity pattern, and treatment changes based on the sensitivity pattern in a case record form. AM sensitivity testing was performed by the modified Kirby Baur method as recommended by clinical and laboratory standard institute (CLSI). Internal and external quality control were maintained for culture and sensitivity method.*
Results: *The most commonly isolated organisms were Klebsiella pneumoniae (28.6 %) and Pseudomonas aeruginosa (16.3 %). Lower respiratory tract infection (LRTI) was the most common infection. Imipenem, meropenem and levofloxacin were the most effective antimicrobials for Gram-negative isolates (GNIs) while vancomycin ciprofloxacin, and gentamicin were the most efficacious antimicrobials for Gram-positive isolates (GPIs). Widespread resistance to third generation cephalosporins and cloxacillin was noted for GNIs and GPIs, respectively. Meropenem (100 %) > levofloxacin (100 %) > sparfloxacin (94.4 %) > gentamicin (83.3 %) was the rank order of antimicrobial activity against LRTI.*
Conclusion: *GNIs were the predominant cause of infection in ICUs. Third generation cephalosporins-resistant GNIs were the predominant resistant organisms. The study showed that fluoroquinolones and aminoglycosides could be used as first line AMs for the effective management of LRTI in a hospital setting.*

Keywords: *Antibiotic sensitivity, Bacterial resistance, Intensive care unit, Tertiary hospital*

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INTRODUCTION

Antimicrobial (AM) resistance is an emerging clinical problem in intensive care units (ICUs), including critical care, neonatal and intensive cardiac care unit. Both AM-resistant Gram-negative bacilli (GNB) and Gram-positive bacteria (GPB) are reported as important causes of hospital-acquired infections [1]. Worldwide, ICUs are faced with increasingly rapid emergence and spread of AM-resistant bacteria because of frequent use of broad-spectrum AMs, crowding of patients with high levels of disease acuity in relatively small, specialized areas of the hospital, shortage of nursing and other supporting staff due to economic pressures (which increases the likelihood of person-to-person transmission of microorganisms) and the presence of more chronically and acutely ill patients who require prolonged hospitalization [1,2]. Indiscriminate and inadequately prolonged use of AMs also leads to emergence and proliferation of resistant strains preferentially [3]. Moreover, AMs are prescribed prophylactically and empirically without carrying out sensitivity studies particularly in developing countries. In ICUs, patients may be immune-compromised and many prosthetics and instrumentations are used routinely.

Nosocomial infections are among the most serious infections acquired by ICU patients [1]. Notable among these are methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), *Clostridium difficile*, extended-spectrum β-lactamase-producing GNB, and *Candida* [4]. Infections caused by these microorganisms increase hospital stay and attributable mortality. Newer resistance, such as New Delhi metalloproteinase (NDM) or carbapenemase, pose fresh challenges. NDM-resistant *E. coli* and *K. pneumoniae* are highly resistant to all AMs, except tigecycline and colistin [5]. If this resistance spreads widely, the important carbapenem group of drugs will be ineffective and would render many infections untreatable.

Prevention of the emergence and dissemination of resistant microorganisms will reduce adverse events and their attendant costs. Appropriate antimicrobial stewardship that includes optimal selection, dose, and duration of treatment, as well as control of AM use, will prevent or slow the emergence of resistance among microorganisms [6]. Development of AM resistance pattern is directly proportional to the volume of AM consumed. Therefore, to reduce the development of AM resistance usage regulation is essential [7]. Monitoring the use of AMs and review of sensitivity patterns are imperative. Audit of AM sensitivity patterns in ICUs and critical care units (CCUs) are crucial and far more important for giving effective treatment and decreasing the spread of resistance.

The present study was, therefore, designed to audit the AM sensitivity pattern of microbial isolates from patients in intensive care units (ICUs) of a tertiary care hospital in India.

METHODS

Setting and design

This retrospective, observational study was carried out in a tertiary care hospital – Sir Takhtsinhji General Hospital, Bhavnagar, India after receiving approval from the Institutional Review Board (IRB), Government Medical College, Bhavnagar, Gujarat, India. Consent waiver was obtained from the IRB for the evaluation of the data.

Data collection

In-patients case files, prescription papers and AM sensitivity reports of two ICUs (critical care unit and intensive cardiac care units) were collected from the case record section of Sir T General Hospital, Bhavnagar, from January 2010 to March 2011. Information collected include the demographic data of the patient, admission unit, duration of hospital stay, diagnosis, and type of infection (nosocomial or primary). Other data collected

include empirical treatment, indication of the use of the AM, collected specimen, causative agent, sensitivity pattern, and treatment following assessment of the sensitivity pattern. The information was entered into a case record form.

The specimens for AM sensitivity testing were studied by Gram stains and culture growth on nutrient, blood and MacConkey agar to identify the isolates. After confirmation of the organism, culture growth was tested for *in vitro*. AM susceptibility testing was performed by disc diffusion method (modified Kirby Bauer method) on Muller Hinton agar. Evaluation by Gram stain, biochemical tests, culture media and disc diffusion methods were carried out daily as per Clinical and Laboratory Standard Institute (CLSI) guidelines [8]. External quality assurance scheme (EQAS) was maintained periodically at Department of Microbiology, Sankara Netralaya, Chennai, India. (EQAS is the process for ensuring that a laboratory i performs to the standard required and therefore provides reliable results).

Data analysis

Data entry was made from the case record from into the Microsoft Excel 2007 program. Descriptive statistics were used to present demographics, infection rate, isolation pattern of various organisms, their antibiogram and prescription pattern of AMs.

RESULTS

Over a period of 15 months, 1007 patients were admitted in the two ICUs with 133 cultures from 80 patients **(**54 males and 26 females) for laboratory tests. Out of these, organisms were isolated from 49 cultures taken from 39 patients (27 male and 12 female), giving an infection rate of 3.87 %. Out of the 80 patients, 16 were discharged (6 of which had positive culture during admission), 5 were referred to a reference centre (3 of which had positive culture during admission), 9 were transferred to general wards (6 of which had positive culture during admission), and 49 died (24 of which had positive culture during admission). No information was available regarding the outcome of one patient.

Of the 49 cultures, 14 were Gram-positive and 35 Gram-negative. The specimens assessed were: blood (44), endotracheal suction (20), urine (18), sputum (11), pus (9), CSF (7), pleural fluid (6), ascitic fluid (3), catheter tip (3), tracheostomy tube (2). Central line tip, endotracheal swab, endotracheal secretion, intercostal drain (ICD), pelvic aspirate, rectal fluid, rectal swab, abdominal wall tissue, tracheal swab and vaginal swab accounted for 1 specimen each.

The isolation pattern of organisms as well as infection pattern are given in Table 1. The most frequently isolated organisms were *K. pneumoniae* (28.6 %) and *P. aeruginosa* (16.3 %) while the most common infections were lower respiratory tract infections or LRTIs (40.8 %) and septicemia (26.5 %). Organisms that caused LRTI the most were *K. pneumoniae* (18.4 %) and *P. aeruginosa* (10.2 %).

The sensitivity pattern of AM agents for Gram-negative (GNIs) and Gram-positive (GPIs) isolates are presented in Tables 2 and 3, respectively.

All Gram-negative isolates were 100 % sensitive to levofloxacin, imipenem and meropenem. The 3rd generation cephalosporins were widely resistant to *K. pneumoniae.* Cefoperazone was 50 % and ceftazidime 0% sensitive to *P. aeruginosa.* Both *Staph epidermidis and Staph aureus* were 100 % sensitive to vancomycin, ciprofloxacin and gentamicin. Higher resistance to macrolides was found for *S. aureus* than for *S. epidermidis.*

Table 1: Infection rate and isolation pattern of various organisms. (Data are expressed in absolute numbers of the organisms with % values in parenthesis)

Organism	LRTIs	Septice-mia	Urinary tract infection	Wound/ tissue infection	Menin-gitis.	Diarr-hea	Total
K. pneumonia	9 (18.37)	2 (4.08)	1 (2.04)	1 (2.04)	1 (2.04)	-	14 (28.57)
P. aeruginosa	5 (10.20)	-	2 (4.08)	1 (2.04)	-	-	8 (16.33)
S. epidermidis	2 (4.08)	5 (10.20)	-	-	-	-	7 (14.29)
A. baumannii	2 (4.08)	3 (6.12)	1 (2.04)	-	-	-	6 (12.24)
E. coli	-	-	3 (6.12)	2 (4.08)	-	1 (2.04)	6 (12.24)
S. aureus	-	2 (4.08)	1 (2.04)	1 (2.04)	-	-	4 (8.16)
β hemolytic *streptococci*	1 (2.04)	-	-	-	-	-	1 (2.04)
Non Hemolytic *Streptococci*	-	1 (2.04)	-	-	-	-	1 (2.04)
P. vulgaris	1 (2.04)	-	-	-	-	-	1 (2.04)
Peptostreptococci	-	-	-	1 (2.04)	-	-	1 (2.04)
Total	20 (40.82)	13 (26.53)	8 (16.32)	6 (12.24)	1 (2.04)	1 (2.04)	49 (100)

Table 2: Antibiogram of Gram-negative organisms (% data with proportion in brackets)

Antimicrobial agent	% Sensitivity			
	K. pneumoniae	***P. aeruginosa***	***E. Coli***	***A. baumannii***
Ciprofloxacin	78.57 (11/14)	87.5 (7/8)	66.66 (4/6)	83.33 (5/6)
Ofloxacin	92.31 (12/13)	85.71 (6/7)	75 (3/4)	100 (5/5)
Levofloxacin	100 (14/14)	100 (7/7)	100 (4/4)	100 (6/6)
Gentamicin	100 (7/7)	100 (7/7)	100 (3/3)	80 (4/5)
Netilmicin	60 (3/5)	66.66 (2/3)	100 (3/3)	66.66 (2/3)
Amikacin	66.66 (4/6)	75 (3/4)	100 (3/3)	100 (4/4)
Tobramycin	69.23 (9/13)	57.14 (4/7)	75 (3/4)	100 (6/6)
Imipenem	100 (13/13)	100 (7/7)	100 (4/4)	100 (6/6)
Meropenem	100 (14/14)	100 (7/7)	100 (4/4)	100 (6/6)
Cefotaxime	28.57 (2/7)	50 (2/4)	66.66 (2/3)	80 (4/5)
Ceftriaxone	16.66 (1/6)	75 (3/4)	50 (1/2)	75 (3/4)
Ceftazidime	16.66 (1/6)	0 (0/4)	33.33 (1/3)	50 (2/4)
Cefoperazone	16.66 (1/6)	50 (2/4)	66.66 (2/3)	75 (3/4)
Ampicillin+Sulbactam	22.22 (2/9)	0 (0/4)	0 (0/5)	40 (2/5)
Piperacillin	100 (1/1)	0 (0/1)	50 (1/2)	NT
Piperacillin+Tazobactam	100 (2/2)	0 (0/1)	100 (2/2)	NT
Chloramphenicol	66.66 (2/3)	50 (1/2)	50 (2/4)	100 (1/1)
Colistin	0 (0/2)	100 (1/1)	0 (0/2)	NT

Table 3: Antibiogram of Gram-positive organisms (% data with proportion in brackets)

Antimicrobial agent	**% Sensitivity**	
	S. aureus	***S. epidermidis***
Penicillin	0 (0/2)	25 (1/4)
Cloxacillin	50 (2/4)	71.42 (5/7)
Vancomycin	100 (4/4)	100 (7/7)
Cotrimoxazole	25 (1/4)	60 (3/5)
Clindamycin	75 (3/4)	80 (4/5)
Ciprofloxacin	100 (4/4)	100 (6/6)
Ofloxacin	50 (1/2)	100 (2/2)
Gentamycin	100 (2/2)	100 (4/4)
Amikacin	50 (1/2)	100 (3/3)
Tetracycline	50 (1/2)	100 (3/3)
Erythromycin	50 (2/4)	42.85 (3/7)
Roxithromycin	100 (2/2)	50 (2/4)
Clarithromycin	100 (1/1)	33.33 (1/3)
Azithromycin	100 (2/2)	75 (3/4)

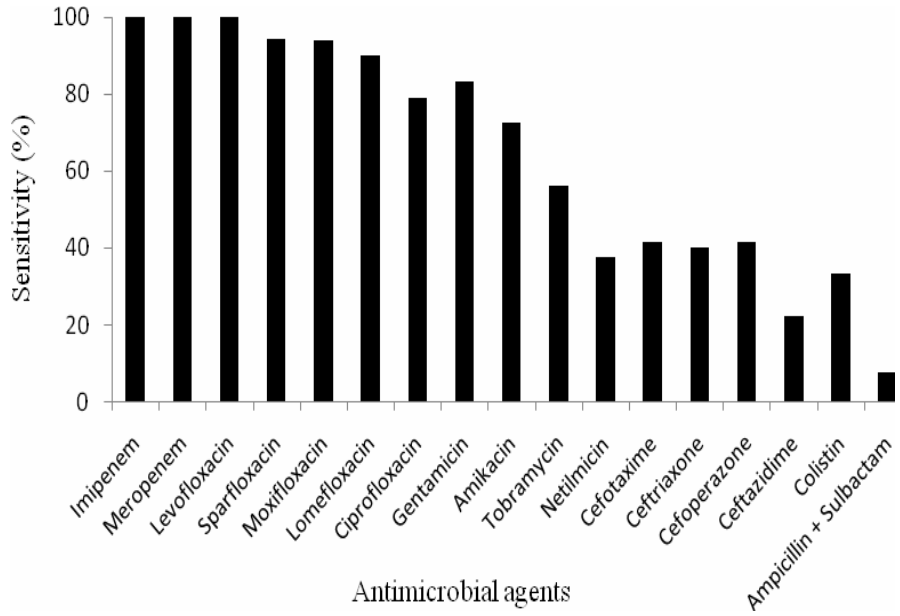

Figure 1: Sensitivity of antimicrobial agents (AMs) to lower respiratory tract infections (LRTIs)

The sensitivity pattern of organisms causing LRTI is shown in Figure 1. Imipenem, meropenam, levofloxacin (each 100 %), sparfloxacin (94.4 %), moxifloxacin (94.1 %), lomefloxacin (90.0 %) and gentamicin (83.3 %) were effective AMs for LRTIs; while imipenem, meropenem, vancomycin, levofloxacin, sparfloxacin, and gentamicin showed 100 % sensitivity to the causative organisms in septicemia. The prescription pattern of AMs is presented in Table 4. The most frequently used drugs were metronidazole (58.8 %), cefotaxime (50.0 %), ciprofloxacin (32.5 %), levofloxacin (28.8 %) and ceftriaxone (27.5 %).

Table 4: Prescription pattern of antimicrobial agents in two intensive care units (ICUs)

Antimicrobial agent	Patient (%)
Metronidazole	58.8
Cefotaxime	50.0
Ciprofloxacin	32.5
Levofloxacin	28.8
Ceftriaxone	27.5
Amikacin	20.0
Piperacillin/Tazobactam	18.8
Ampicillin	11.3
Crystalline Penicillin	11.3
Gentamicin	10.0
Amoxicillin + Clavulanic acid	8.8
Vancomycin	6.3
Azithromycin	6.3
Ofloxacin	5.0
Cefuroxime axetil	3.8
Meropenem	2.5
Tobramycin	2.5
Ceftazidime	2.5
Cefoperazone + Sulbactam	1.3
Trimethoprim	1.3
Clindamycin	1.3
Cloxacillin	1.3
Ceftriaxone + Sulbactam	1.3
Sulfmethoxazole	1.3
Linezolid	1.3
Lincosamide	1.3

DISCUSSION

Antimicrobial agents (AMs) are among the most commonly used drugs in hospitalized patients. The emergence of AM resistance in ICUs is of great concern as it increases the likelihood of drug interactions/side effectsand cost of therapy due to use of newer antibiotics. Resistance may also be responsible for prolonged hospital stays and can affect prognosis. The problem of resistance in a hospital is difficult to understand without the knowledge of AM use pattern [9]. Monitoring the use of AM and review of sensitivity pattern are, therefore, important.

Organisms were isolated in 36.8 % out of cultures investigated, compared to 64.7 % in an Indonesian ICU [10]. The most common infections in our study were LRTI and septicemia as against urinary tract infection and wound infections from another Indian study [11]. *K. pneumoniae* was the predominant organism isolated from this study compared with in earlier studies which indicated *S. aureus* [12], *E. coli* [11] and *P. aeruginosa* [10], respectively. *K. pneumoniae* was the predominant organism isolated from LRTI as against *Streptococcus* [11], *P. aeruginosa* [13], and non-fermentative GNB [14] found in other studies. Thus, the isolation pattern of organisms appear to vary with time and hospital settings. Our data showed that there were more Gram-negative than Gram-positive isolates. This is not surprising since the former are known to develop resistance more rapidly and extensively than the latter [15,16].

With regard to GNIs, *K. pneumoniae* was the most common isolate, mainly from instrument-associated infections. Most studies on carbapenems resistance have been carried out on GNIs, especially *P. aeruginosa* and *A. baumannii* [17-20]. We did not find any carbapenem resistant isolates in our study. Various other studies found carbapenem resistance by *A. baumannii*, *P. aeruginosa* and *K. pneumoniae* [1,7,10,17, 18,21]. Non-isolation of carbapenem-resistant Gram-negative bacteria (GNB) in our study may be due to its restricted use as a reserve drug in the ICUs used. Only 7.37 % of patients received meropenem and none received imipenem.

In our study, *K. pneumoniae* has a similar sensitivity pattern with third-generation cephalosporins found in an Indian study [11]. This shows reduced sensitivity of third-

generation cephalosporins towards *K. pneumoniae*. The resistance of *K. pneumoniae* to cephalosporin is usually due to breakdown of the drug by extended-spectrum beta-lactamases (ESBL) [22,23]. Infection with ESBL organisms is associated with increased hospital stay and increased cost of management [23]. Among the aminoglycosides, gentamicin was the most effective, followed by tobramycin and amikacin. In an earlier study, the order was amikacin followed by gentamicin and tobramycin [11]. The difference may be due to greater use of amikacin than gentamicin. Although tobramycin was the least used among the aminoglycosides, it showed about the same resistance as amikacin. This may be due to the development of cross-resistance to both drugs.

In our study, we found higher sensitivity of *P. aeruginosa* to flouroquinolones and aminoglycosides. This suggests that levofloxacin, ciprofloxacin, ofloxacin and gentamicin are the most effective drugs for *Pseudomonas* infections. Anti-pseudomonas agents such as cefoperazone, ceftazidime and piperacillin + tazobactam were largely ineffective, hence their use should be discouraged.

AM resistance to *P. aeruginosa* develops rapidly under selection pressure. The mechanisms of resistance to third generation cephalosporins, carbenicillins and ureidopenicillins are production of AmpC β-lactamases, class A carbenicillin hydrolysing β-lactamases, class A ESBL and DNA gyrases, active efflux pumps and diminished permeability of the outer membrane [24,25]. Comparison of the sensitivity pattern for *E. coli* in our study to those of other studies [7,11-13,17] suggests that *E. coli* has a comparatively higher sensitivity to cefotaxime, cefoperazone, gentamicin, amikacin, ciprofloxacin and levofloxacin. We found two colistin-resistant isolates of *E. coli.*

Acinetobacter is a new emerging organism in nosocomial infection that has been reported in many studies to be widely resistant. We, however, found comparatively good sensitivity for *A. baumannii.* [7,11].

For GPIs, both *S. epidermidis and S. aureus showed* almost full resistance to penicillin. Varying levels of resistance of the various penicillins to *S. aureus* and *S. epidermidis* have been reported in studies carried out in ICUs in India, Netherlands and Canada [7,12,26,27]. One study showed that 41.2% isolate of *S. aureus* were resistant to vancomycin [10]. This may be due to minimal use of vancomycin in our setup as only 6.25% of patients received vancomycin. Our study found higher sensitivity of *S. aureus* to ciprofloxacin, gentamicin, clindamycin, azithromycin and erythromycin than was reported in the studies [7,11]. A similar finding in respect of *S. epidermidis* is noted for ciprofloxacin, gentamicin [7] but the reverse was the case with regard to the sensitivity of *S. epidermidis* to the macrolides (erythromycin and azithromycin) and clindamycin [7]. This suggests that coagulase-negative *Staphylococci* showed more resistance in the setting of our study.

The carbapenems exhibited complete sensitivity towards LRTI isolates in our study unlike the increasing resistance reported previously for various GNIs [13]. No cross-resistance was seen among the aminoglycosides, and gentamicin was the most effective among them. Thus, the fluoroquinolones and gentamicin can be used as first-line drugs, with the carbapenams as second-line agents. Since the 3rd generation cephalosporins were very ineffective due, possibly, to their frequent use in the ICUs studied, their use should be restricted. The amount and pattern of antibiotic use contribute to the development of resistance [28]. Antibiotic cycling should be carried out to reduce selection pressure and further resistance to third generation cephalosporins [29].

Ongoing surveillance of AM susceptibility pattern helps in the preparation and regular review of local guidelines for the empirical selection of first-line AM agents [1,30]. Infection with resistant organisms can be associated with poor prognosis if the initial antibioticused does not provide adequate coverage [29]. Newly admitted patients should be screened for target organisms. AMs should be altered based on sensitivity results or stopped altogether if no organism has been isolated and the clinical picture of patients permit it [29].

Limitations of the study

Antibiotic disc sensitivity test results may vary with hospital setting, while infection rate in a hospital may depends on the hospital environment, antibiotic use and other infection control practices. All these would limit the applicability of the findings of this study to other hospital settings.

CONCLUSION

K. pneumoniae is the predominant isolated organism and LRTI the predominant infection in the ICUs studied. Cloxacillin-resistant *S. aureus* and *S. epidermidis* and third generation cephalosporin-resistant GNB are predominant antimicrobial-resistant organisms found. The fluoroquinolones and gentamicin can be used as first-line drugs, with the carbapenams as second-line agents. Since the 3rd generation cephalosporins are very ineffective due, possibly, to their frequent use in the ICUs studied, their use should be restricted..

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