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An Appraisal of Sensitivity and Resistance Pattern of Organisms Isolated from Hospital Acquired Pneumonia Patients.

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ABSTRACT

Hospital acquired pneumonia (HAP) is an infection of lung parenchyma develops at least after 48 hours of hospitalization for another illness or procedure, also known as nosocomial pneumonia. Organisms causing HAP were found in 221 (43.7%) out of 505 patients. The most common isolates found were *Klebisiella pneumonia* (30.9%) *Acinetobacter species* (29.4%), *Pseudomonas aeruginosa* (16.7%), *Escherichia coli* (9.1%) and methicillin resistant *Staphylococcus aureus* (MRSA; 3.7%, 73%). Sensitivity pattern of gram negative organisms such as *Klebisiella pneumonia, Acinetobacter species* and *Escherichia coli* was comparatively identical showing high sensitivity towards colistin and tigecycline where as *Pseudomonas aeruginosa* was highly sensitive to only colistin. Among Ggram positive organisms MRSA was highly sensitive to linezolid, tetracycline and cotrimoxazole, methicillin sensitive *Staphylococcus aureus* to (MSSA) cotrimoxazole (80%) and tetracycline (71.4%) and *Streptococcus pneumonia* to chloramphenicol, penicillin, piperacillin, cefoperazone-sulbactam and colistin. Sensitivity pattern of Gram negative organisms was different from that of Gram positive organisms causing high mortality rates. Among Gram positive organisms MRSA caused mortality as twice as that of MSSA. Multidrug resistant strains were resulted by inappropriate and inadequate antibiotic therapy, causing high rate of morbidity mortality and adding cost to therapy which is the major concern in recent times.

Keywords: Hospital acquired pneumonia, *Klebisiella pneumonia,* Antibiotic, Mortality and Multidrug resistant strains.

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INTRODUCTION

Hospital acquired pneumonia (HAP) is an infection of lung parenchyma that develops after 48 hours of hospitalization for another illness or procedure, also known as nosocomial pneumonia [1].The incidence of HAP in ICUs varies from 9-24% associated with the care presented and the differences in diagnostic techniques used. The incidence of HAP varies from hospital to hospital due to the difference in study population, hospital setting and diagnostic criteria used to confirm pneumonia [2]. Hospital acquired pneumonia (HAP) is the second most common nosocomial infection and associated with high mortality rate [3]. *Pseudomonas aeruginosa* and *Acinetobacter* spp (*eg*, *Acinetobacter calcoaceticus* and *Acinetobacter baumannii*) which are resistant to many antibiotics and account for 30 to 50% of HAP which are evolving into multidrug resistant (MDR) strains [3-5].

MDR strains usually first evolve in the areas where the antimicrobials usage is high [6] such as intensive care units and emergency units. Treating the infections caused by these MDR strains is the most challenging step in the therapy. HAP still remains an important cause of morbidity and mortality, which is even more when HAP caused by MDR organisms like *Pseudomonas aeruginosa, Acinetobacter species, Klebisiella pneumonia* and methicillin resistant *Staphylococcus aureus* especially in the elderly patients [7]. HAP needs an appropriate antibiotic therapy along with intensive care unit management [5,8]. The mortality rate is much higher when the empirical antibiotic therapy is inappropriate and inadequate [6].

Need for the study:

Although antibiotics have been in use since 1940's, especially in treating the respiratory tract infections like pneumonia, it is becoming increasingly difficult on account of steady increase in antibiotic resistance, emerging of MDR strains and a simultaneous decline in the number of newer antibiotics being developed which come at a higher cost. Hence there is an extensive need to analyze sensitivity and resistance pattern of organisms not only in HAP patients but also in all the infectious diseases in each hospital settings for implementation of definite and rational antibiotic therapy in order to prevent the further evolution of resistant strains and to reduce patient morbidity, mortality and hospital cost.

The principle objectives of the study are to identify organism isolated in HAP patients and to analyze the sensitivity and resistance pattern of isolates.

MATERIALS AND METHODS

A prospective observational study, carried out in Kasturba Hospital, Manipal. HAP patients who fulfill the inclusion criteria (e.g., patients admitted to hospital/ICU for more than 72 hours, patients whose diagnosis was confirmed by chest X-ray or by culture as pneumonia and aged above 18 years) were identified during daily visits to the emergency wards & enrolled into the study after taking informed consent. Patients were followed from the day of diagnosis of HAP, till the day of discharge or death. The patient data like demography (name, age, sex),

medical history, medication history, diagnosis, co-morbid disease, etiological factors, vital signs, diagnostic test report, , microbiological reports (Gram stain and culture sensitivity) drug treatment chart with dose and duration of treatment and clinical outcome will be recorded in the patient case record forms (CRFs).

The antimicrobial resistance and susceptibility pattern was assessed based on the culture sensitivity report. WHONET Version 5.6 was used for compilation and analysis culture sensitivity data. Based on the sensitivity and resistance pattern, an antibiogram was prepared to describe the sensitivity and resistance pattern for each organism and antibiotics that were used in the hospital

Data Analysis: Microorganism sensitivity, resistance were expressed in percentage

RESULTS

The mean age of study population was 55.1±16.2 years and 38.4% of patients were more than 60 years of age (Table 1). The majority of patients were males n=338 (66.9%) and male to female ratio was 2:1. Among 505 HAP patients, 386 improved and were discharged; remaining 119 patients expired. Mortality rate in HAP patients was 23.6%.

Table 1: Demographic characteristics and outcome of HAP patients

Characteristics	Total number of HAP Patients (n=505)
Mean age±SD, years	55.1±16.2
Age> 60 years, n (%)	194 (38.4%)
Male sex, n (%)	338 (66.9%)
Smoking, n (%)	133 (26.3%)
Alcohol, n (%)	103 (20.4%)
Recovered, n (%)	386 (86.7%)
Mortality, n (%)	119 (23.6%)

Different types of HAP

Clinical type of HAP patients included in the study was given in Table 2. Ventilator associated pneumonia was the most common (VAP) 230 (45.5%), followed by aspiration pneumonia 146 (28.9%) and post-operational pneumonia 123 (24.4%).

Table 2: Type of hospital acquired pneumonia

Type of HAP	Frequency	Percentage
Aspiration	146	28.9
Ventilator associated (VAP)	230	45.5
Post-operational	123	24.4

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Isolated pathogens

Out of 505 HAP patients culture and sensitivity was done for 251 (49.7%) patients and isolates were found in 221 patients, rest were showing no growth (Table 3). The different pathogens isolated from 221 patients were *Klebsiella pneumonia*, *Acinetobacter species*, *Pseudomonas aeruginosa*, *Escherichia coli*, methicillin resistant *Staphylococcus aureus* (MRSA), methicillin sensitive *Staphylococcus aureus (MSSA)*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Enterobacter* species and *Burkholderia* species (Table 4). *Klebsiella pneumonia* (30.9%) was the most common pathogen, followed by *Acinetobacter* species *(29.4%)*, *Pseudomonas aeruginosa* (16.7%). Majority of the patients, 132 (26.1%) were infected with single organism. Two or more organisms were isolated from 89 (17.6%) of patients. Mortality was highest in patients infected with *Pseudomonas aeruginosa* (93%) and MRSA (73%).

Table 3: Culture sensitivity tests done among HAP patients

Sr. No	Culture Sensitivity		No. of patients	Percentage (%)
1	Done	Isolates found	221	43.7
		Sterile	30	5.9
2	Not done		254	50.3
Total			505	100

Table 4: Pathogens isolated from HAP patients

Organism	Isolate (Total=221)	Percentage (%)	Mortality (%)
Klebsiella pneumoniae	68	30.76	53
Acinetobacter species	65	29.4	68
Pseudomonas aeruginosa	37	16.7	93
Escherichia coli	20	9.1	33
MRSA	6	2.7	73
MSSA	5	2.26	36
Streptococcus pneumoniae	4	1.81	22
Haemophilus influenzae	6	2.7	33
Enterobacter species	5	2.26	38
Burkholderia species	5	2.26	10

MRSA= Methicillin resistant *Staphylococcus aureus*
MSSA=Methicillin sensitive *Staphylococcus aureus*

Analysis of sensitivity and resistance pattern of isolated organisms from HAP patients:

Cumulative analysis of sensitivity and resistance pattern of isolated microorganism from HAP patients were done based on the culture and sensitivity reports.

Sensitivity and resistance pattern of *Klebsiella pneumoniae*:

Sensitivity and resistance pattern of *Klebsiella pneumoniae* against various antimicrobial agents is summarized in Figure 1. *Klebsiella pneumoniae* was found to be highly

sensitive to colistin, tigecycline (100%) followed by amikacin (64.9%) and it was more resistant to ampicillin (90.3%) followed by amoxicillin-clavulanate (77.4%), ticarcillin-clavulanate (73.1%), cefuroxime (71%) and cefepime (70.4%).

***Acinetobacter* species sensitivity and resistance pattern:**

Sensitivity and resistance pattern of *Acinetobacter* species against various antimicrobial agents is summarized in Figure 2. *Acinetobacter* species was completely sensitive to tigecycline followed by colistin (96.1%) and was almost equally resistant to amikacin, amoxicillin-clavulanate, ampicillin, cefazolin, ceftriaxone, cefuroxime, ciprofloxacin, cotrimoxazole, gentamicin, aztreonam, cefepime, meropenem, piperacillin-tazobactum, ticarcillin-clavulanate.

***Pseudomonas aeruginosa* sensitivity and resistance pattern:**

Sensitivity and resistance pattern of *Pseudomonas aeruginosa* against various antimicrobial agents is summarized in Figure 3. *Pseudomonas aeruginosa* was found to be highly sensitive to colistin (87.5%) and was more resistant to aztreonam (63.6%) and cefepime (62.1%).

***Escherichia coli* sensitivity and resistance pattern**

Sensitivity and resistance pattern of *Escherichia coli* against various antimicrobial agents is summarized in Figure 4. *Escherichia coli*. showed complete sensitivity to colistin and tigecycline followed by cefaperazone-sulbactum (84.6%), amikacin (84.6%) and meropenem (83.3%). It was 100% resistant to amoxicillin-clavulanate, ampicillin, cefuroxime and aztreonam followed by ticarcillin-clavulanate (91.7%). sensitivity towards colistin and tigecycline cannot be considered significant as the number of isolates tested were very less.

Sensitivity and resistance pattern of methicillin resistant *Staphylococcus aureus*:

Sensitivity and resistance pattern of methicillin resistant *Staphylococcus aureus* (MRSA) against various antimicrobial agents is summarized in Figure 5. MRSA was completely sensitive to linezolid, tetracycline and cotrimoxazole. It was completely resistant to cefazolin followed by 87.5% with erythromycin, cloxacillin, ciprofloxacin, amoxicillin-clavulanate and ampicillin.

Sensitivity and resistance pattern of Methicillin sensitive *Staphylococcus aureus*:

Sensitivity and resistance pattern of methicillin sensitive *Staphylococcus aureus* (MSSA) against various antimicrobial agents is summarized in Figure 6. MSSA was more sensitive to cotrimoxazole (80%) and tetracycline (71.4%) and was more resistant to erythromycin (83.3%) followed by ampicillin (80%), cefazolin (75%), ceftriaxone (75%), ceftazidime (75%) and cefuroxime (75%).

Sensitivity and resistance pattern of *Streptococcus pneumoniae*:

Sensitivity and resistance pattern of *Streptococcus pneumoniae* against various antimicrobial agents is summarized in Figure 7. *Streptococcus pneumoniae* showed 100% sensitivity towards chloramphenicol, penicillin, piperacillin, cefoperazone-sulbactum and colistin and was 100% resistant to cefuroxime, cotrimoxazole, netilmicin, aztreonam, cefepime, piperacillin-tazobactum and ticarcillin-clavulanate. The significance of resistance and sensitivity pattern in *Streptococcus pneumoniae* was not significant as the number of isolates tested with each antibiotic was significantly less.

Sensitivity and resistance pattern of *Haemophilus influenzae*:

Sensitivity and resistance pattern of *Haemophilus influenzae* against various antimicrobial agents is summarized in Figure 8. *Haemophilus influenzae* was 100% sensitive to amoxicillin-clavulanate, chloramphenicol and ceftriaxone and was equally 33.3% resistant to ampicillin, cotrimoxazole, tetracycline, penicillin and erythromycin. The values of sensitivity and resistance pattern of this organism were not significant as the number of isolates tested were less.

Sensitivity and resistance pattern of *Enterobacter species*:

Sensitivity and resistance pattern of *Enterobacter species* against various antimicrobial agents is summarized in Figure 9. *Enterobacter species* was 100% sensitive to amikacin and meropenem followed by vancomycin (75%). It was 100% resistant to piperacillin-tazobactum, cefepime, cefoperazone-sulbactum, aztreonam, netilmicin, gentamicin, cefuroxime, ceftriaxone, cefazolin, amoxicillin-clavulanate and ampicillin. As the number of isolates tested are less this results might not be significant.

Sensitivity and resistance pattern of *Burkholderia species*:

Sensitivity and resistance pattern of *Burkholderia species* against various antimicrobial agents is summarized in Figure 10. *Burkholderia* species was 100% sensitive to ciprofloxacin and was 100% resistant to amikacin, gentamicin, netilmicin, ticarcillin-clavulanate and colistin.

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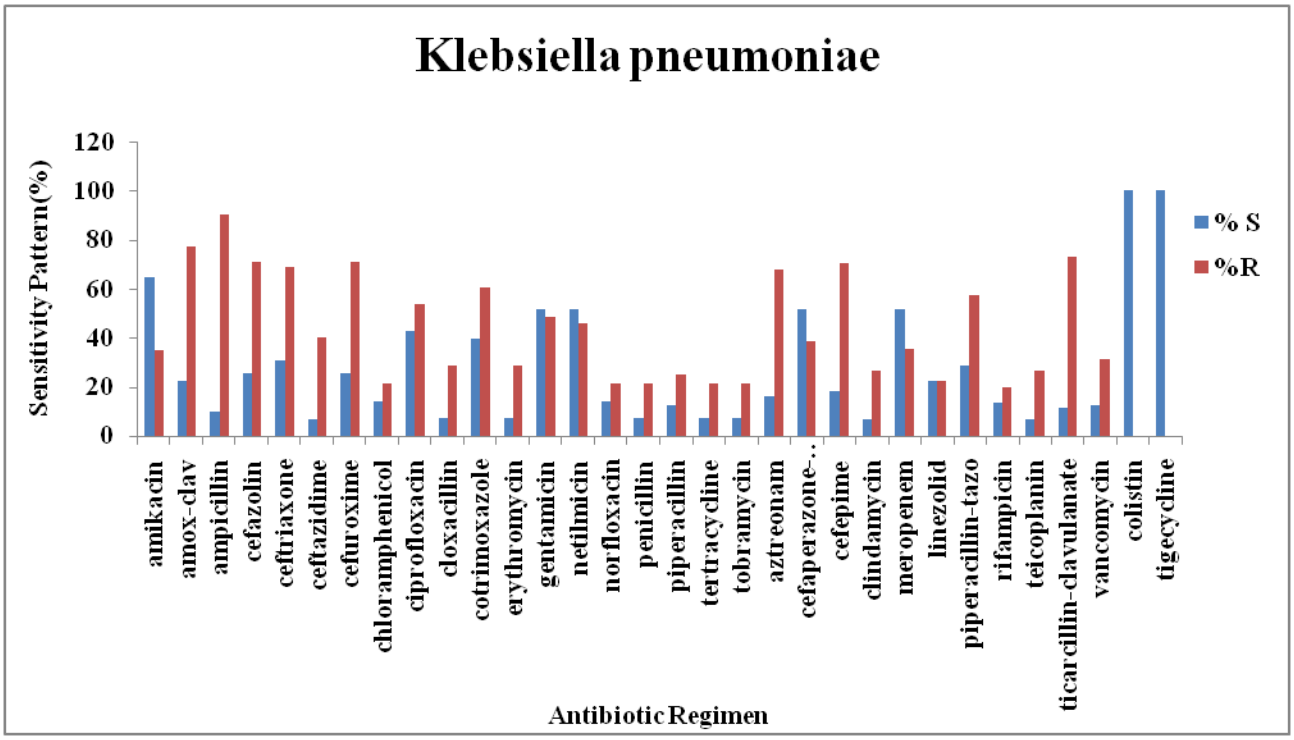

Figure 1: Sensitivity and resistance pattern of *Klebsiella pneumonia*

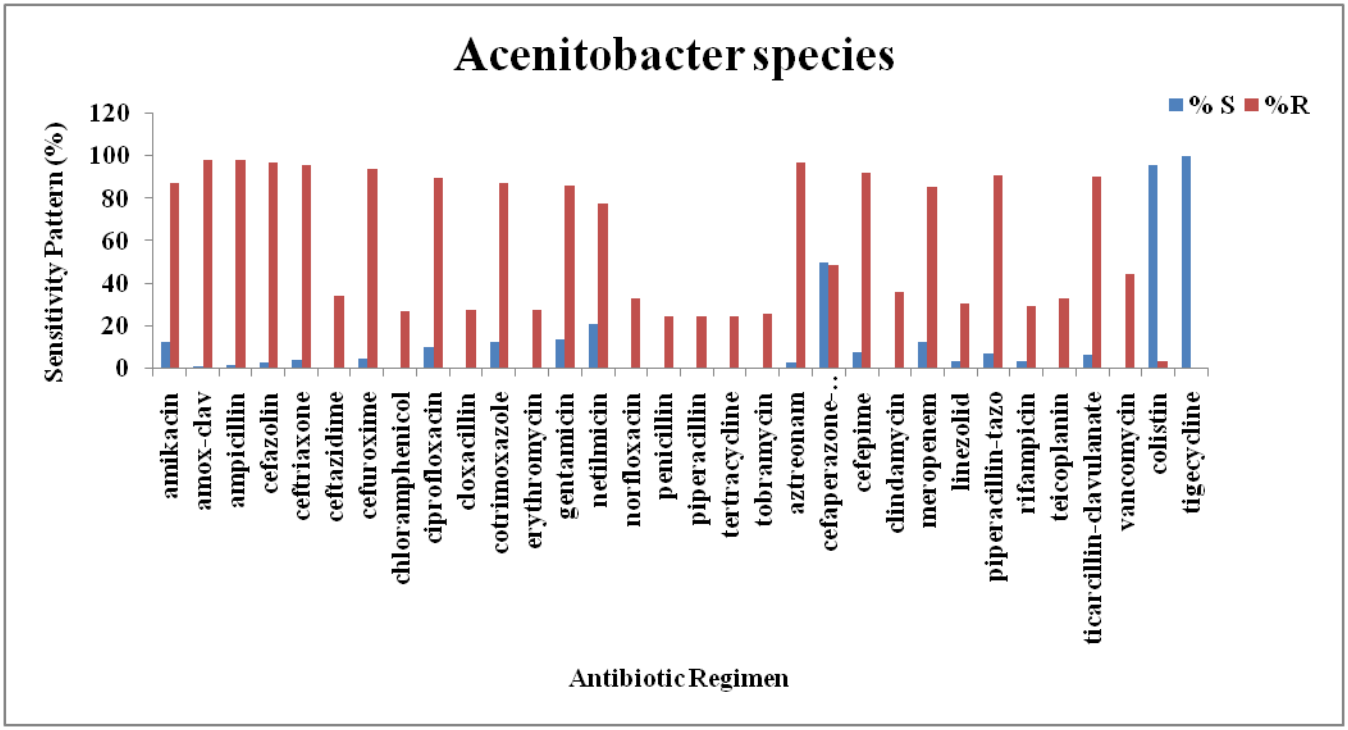

Figure 2: Sensitivity and resistance pattern of *Acinetobacter species*

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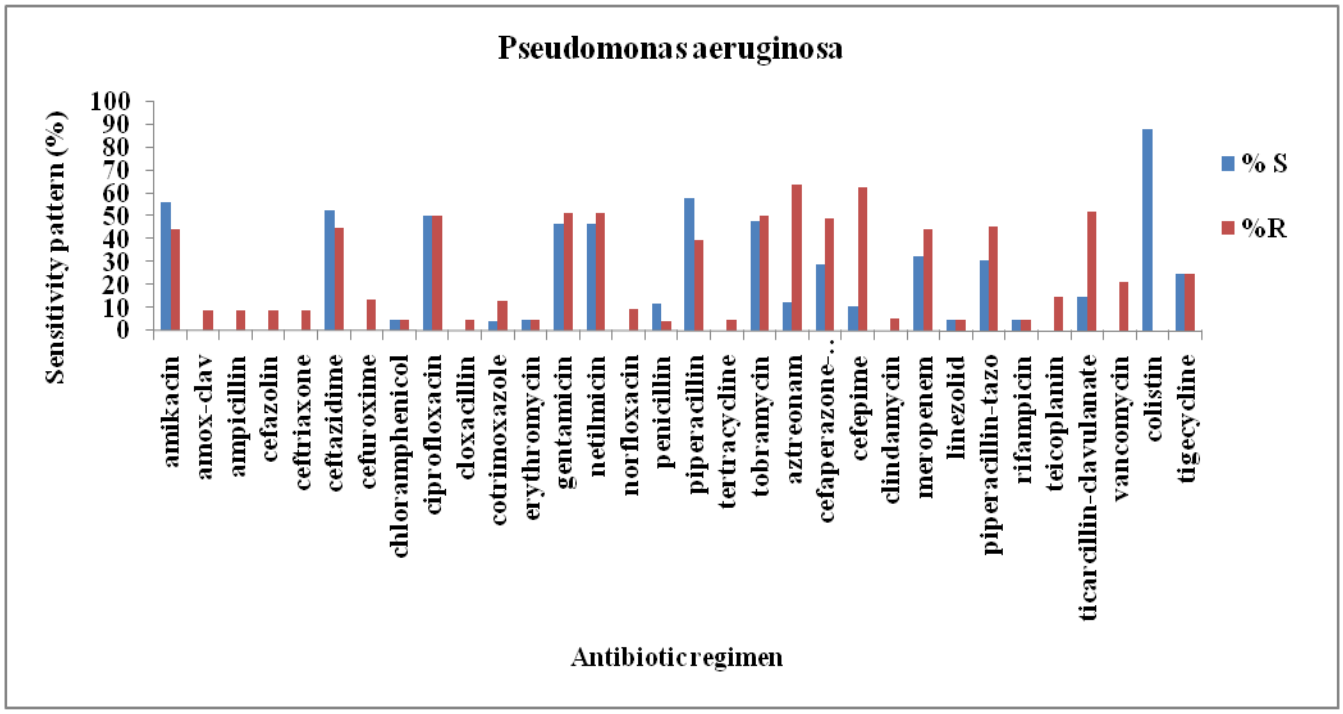

Figure 3: Sensitivity and resistance pattern of *Pseudomonas aeruginosa*

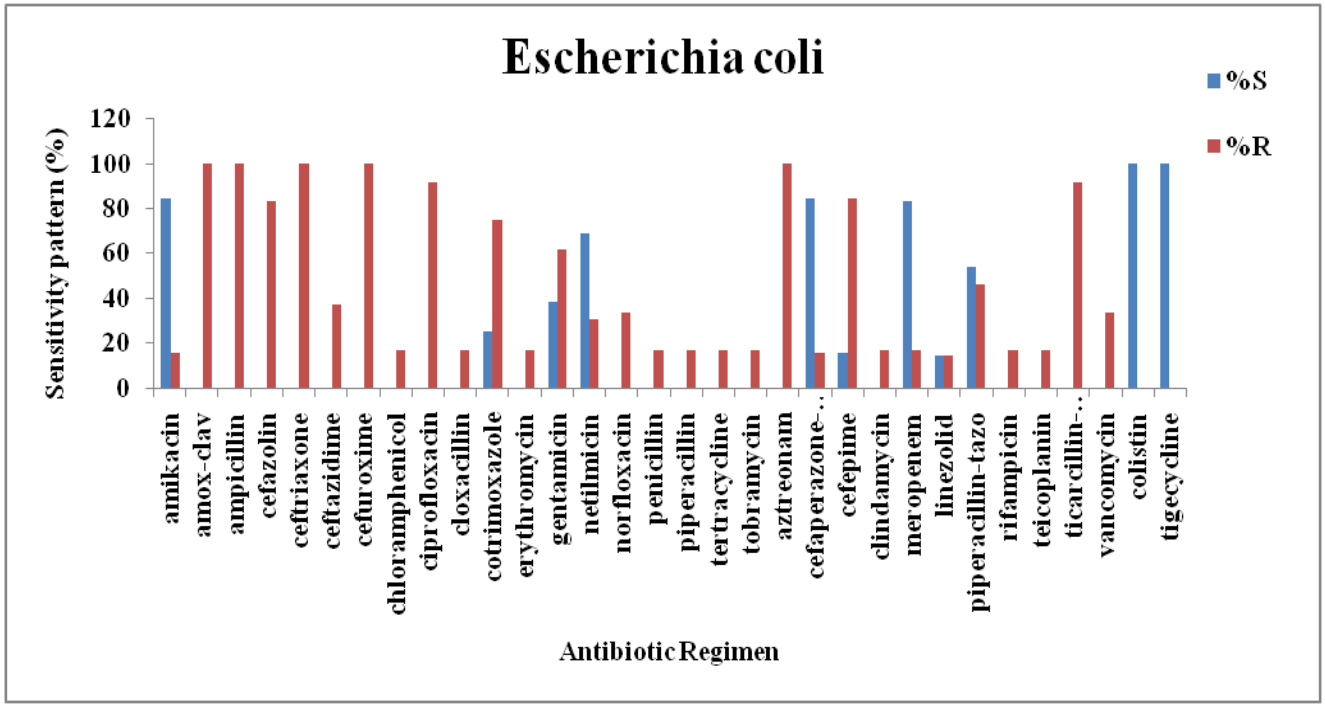

Figure 4: Sensitivity and resistance pattern of *Escherichia coli*

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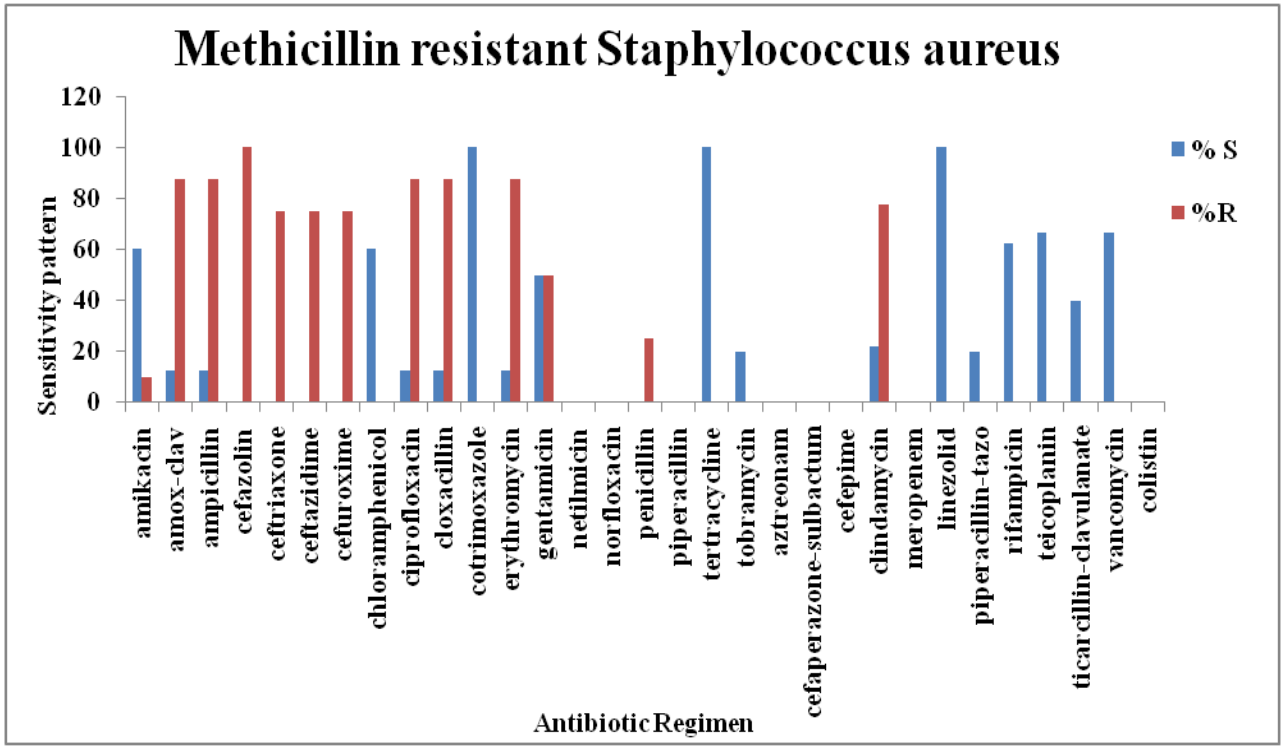

Figure 5: Sensitivity and resistance pattern of Methicillin resistant *S. aureus*

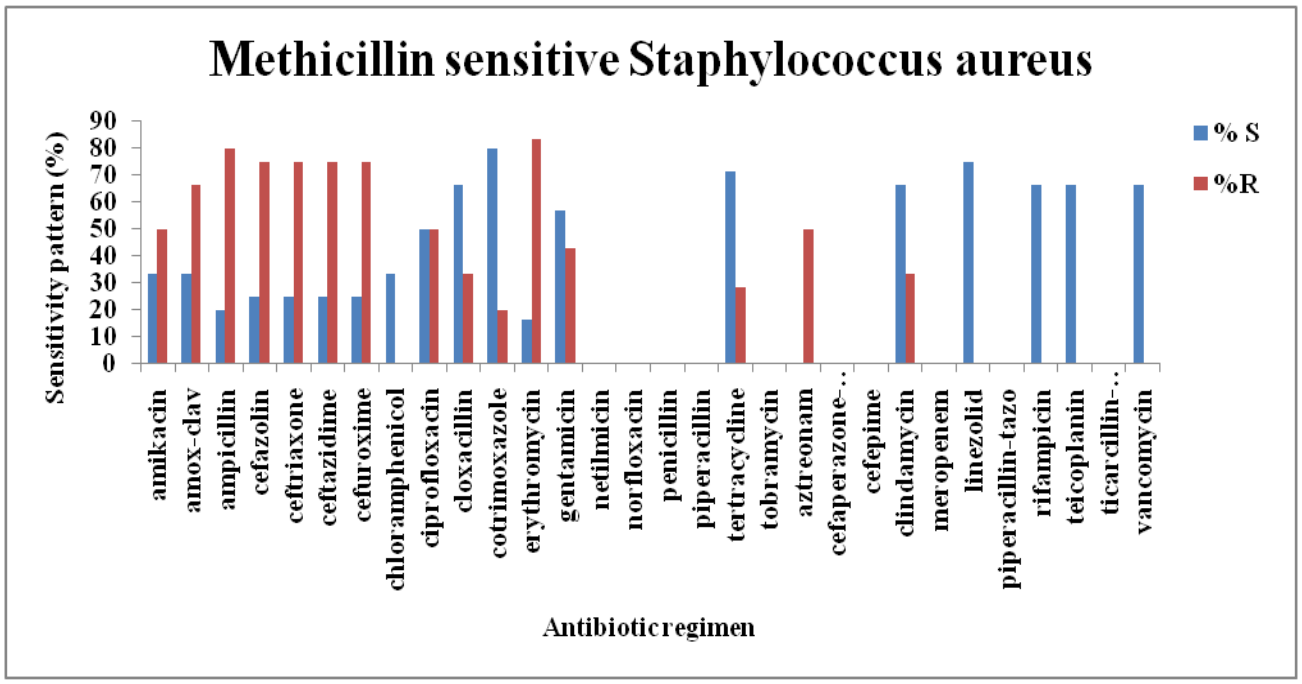

Figure 6: Sensitivity and resistance pattern of Methicillin sensitive *S. aureus*

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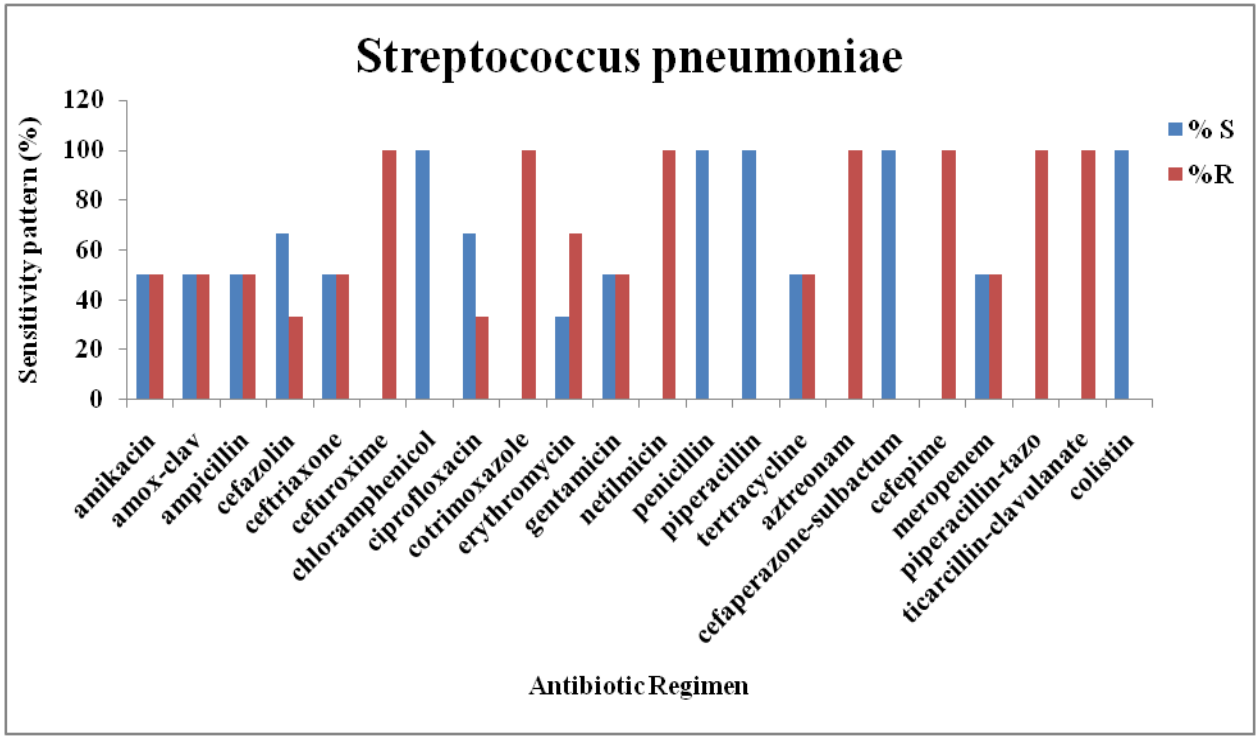

Figure 7: Sensitivity and resistance pattern of *Streptococcus pneumoniae*

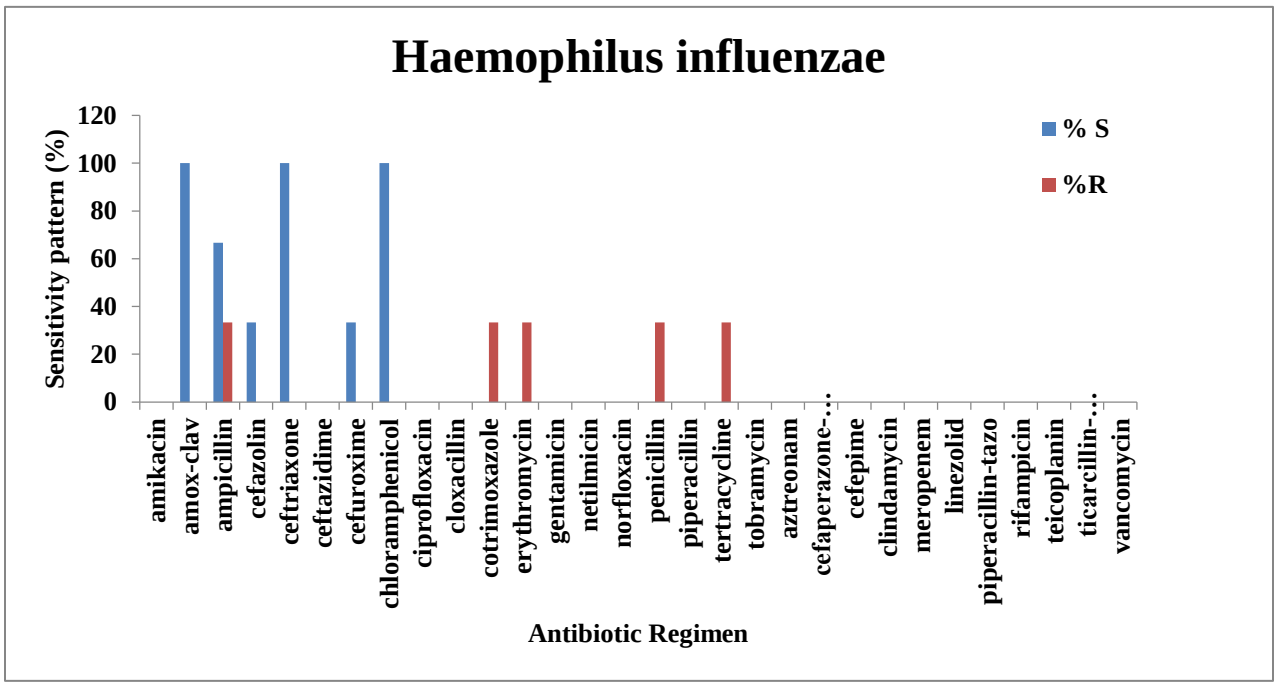

Figure 8: Sensitivity and resistance pattern of *Haemophilus influenzae*

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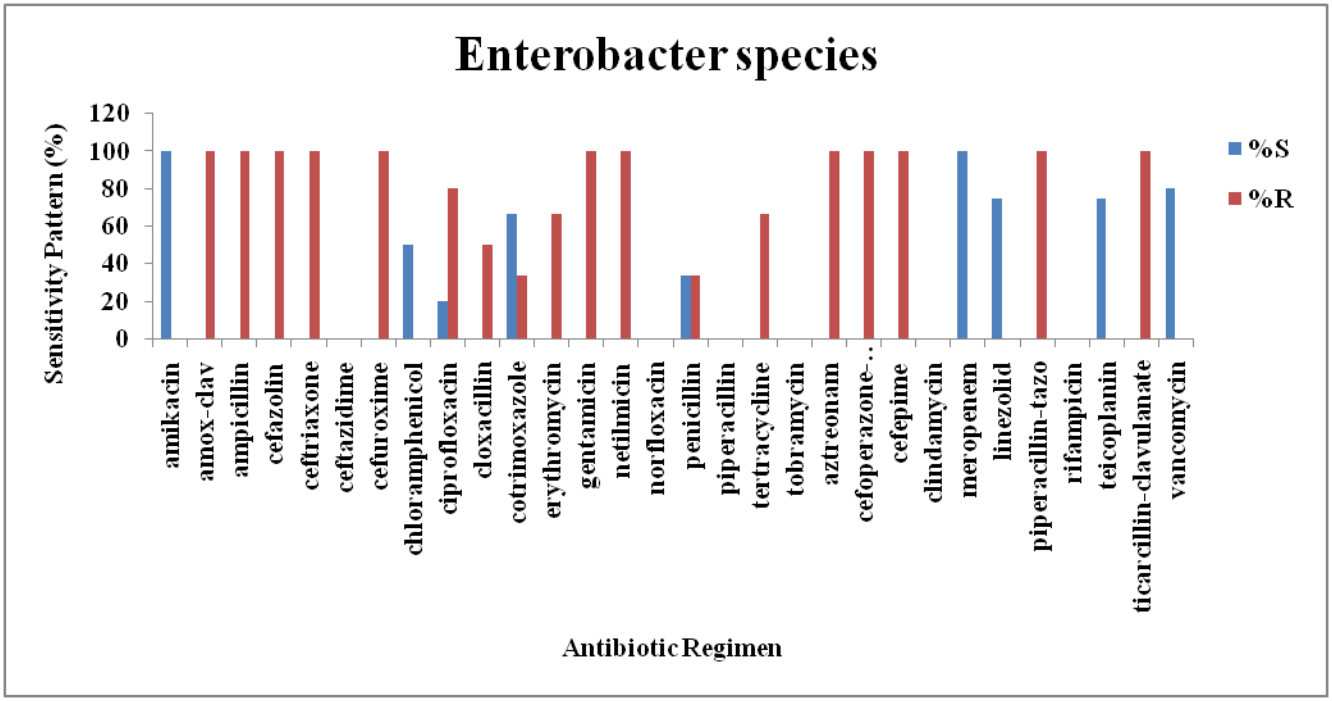

Figure 9: Sensitivity and resistance pattern of *Enterobacter species*

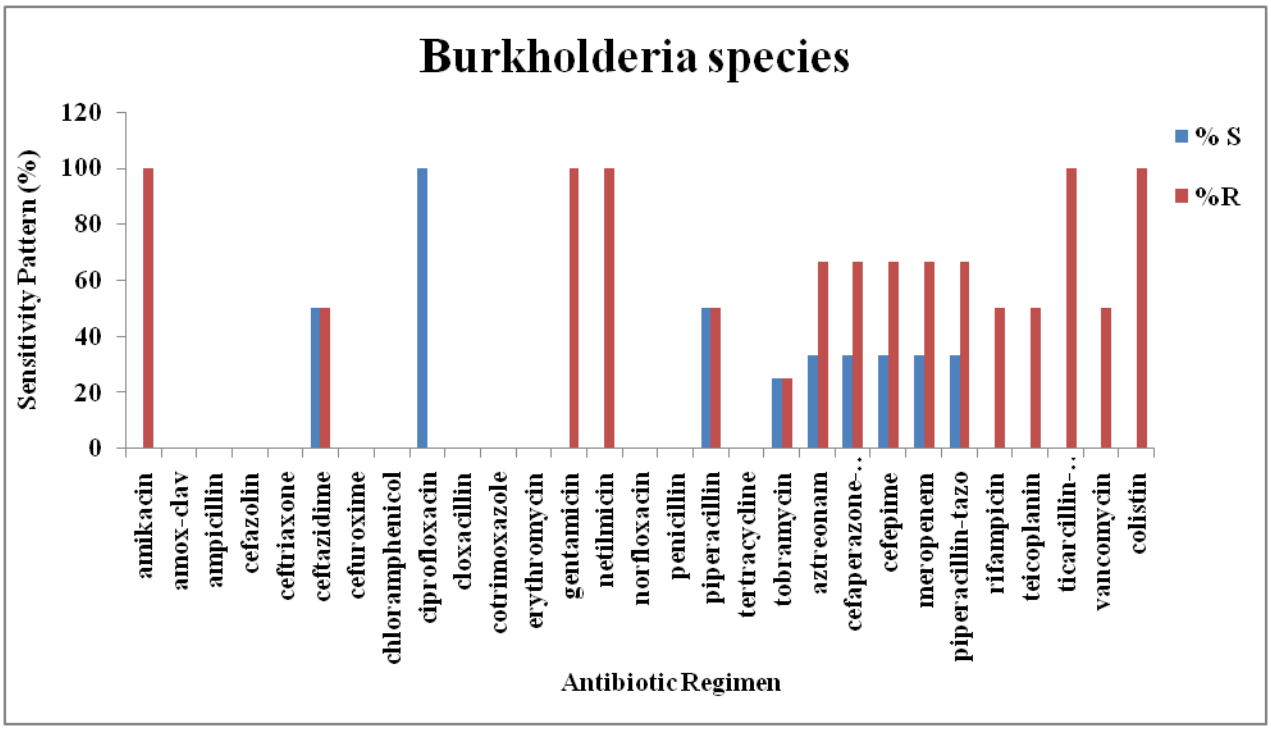

Figure 10: Sensitivity and resistance pattern of *Burkholderia species*

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DISCUSSION

The second most common nosocomial infection is HAP and associated with mortality rate [8]. The identification of organisms and their sensitivity pattern isolated from HAP patients is an important step in selecting adequate and appropriate therapy in order to reduce the morbidity, mortality and the emergence of resistance strains [5, 8]. The selection of definite antibiotic therapy plays an important role in treatment outcomes, especially infection caused by MDR strains.

Among the causative elements that lead to emergence of resistant strains, one of the potential reasons was improper use of antibiotics especially in the ICU settings. Whatever the cause or country of origin, resistant strains can potentially spread across nations and this spread has accelerated in recent times because of increased globalization [9]. Fast growing resistance towards the existing antibiotics and the decrease in the introduction of newer antibiotics is adding to this global problem. There is an urgent need to prevent the emergence of resistant strains.

Apart from these, developing countries like India also contributes heavily to the emergence of resistant strains through inappropriate clinical use of antibiotics and poor infection control in hospitals.

Respiratory tract infections are the most common reasons for antibiotic prescriptions and especially in the case of hospital acquired infections. It is therefore important to evaluate the sensitivity and resistance pattern of microorganisms isolated from infectious disease patients for appropriate use of antibiotics in the clinical setting, to identify steps for rationalizing and restricting the clinical application of antibiotics on the face of growing antibiotics resistance and MDR strains.

A tertiary care hospital has a relatively higher burden from infections and thus, study like ours is most appropriate in the current clinical setting.

In the present study majority of isolates were Gram negative organisms (93.2%) which is similar but at a bit higher than the studies conducted by Alquarshi A M, Fagon *et al* and Simsek *et al* which showing 78.8%, 75% and 72% of Gram negative bacilli respectively among the isolates [10-12].

The most commonly isolated organisms were *Klebsiella pneumoniae* followed by *Acinetobacter* species*, Pseudomonas aeruginosa, Escherichia coli* (Gram negative isolates) and methicillin resistant *Staphylococcus aureus* (Gram positive isolates). This is also similar to previous studies [10,13-15] showing *Klebsiella pneumonia, Pseudomonas aeruginosa* and *Acinetobacter* species are the most common organisms causing HAP.

In our study we observed that *Klebsiella pneumoniae* was found to be highly sensitive to colistin, tigecycline (100%) and amikacin (64.9%), whereas in Alquarshi A M [10] study, it was

more sensitive to aztreonam (100%), imipenem (86.3%) and cefuroxime (82%). The resistant pattern was comparatively similar showing ampicillin (90.3% vs 100%) and amoxicillin-clavulanate [10] (77.4% vs 100%).

Acinetobacter species was totally sensitive to tigecycline, followed by colistin (96.1%) and it was resistant to antibiotics like amoxicillin-clavulanate, ampicillin, cefazolin, cefepime ceftriaxone, cefuroxime, ciprofloxacin, cotrimoxazole, amikacin gentamicin, aztreonam, meropenem, piperacillin-tazobactum and ticarcillin-clavulanate. The study conducted by Patwardhan *et al* [7] showing Acinetobacter species was highly resistant to most of the β-lactam antibiotics (100% resistant to penicillin, amoxicillin, cefotaxime and cefuroxime) aminoglycosides (100% resistant to clindamycin followed by 96.2 % to amikacin, gentamicin and streptomycin) quinolones(96.2% resistant to ciprofloxacin) and tetracyclines(100% resistant to tetracycline). Whereas in the study of Edis, *et al* [16] *Acinetobacter* spp were 93% sensitive to netilmicin followed by cefepime (69%) and was highly resistant to cefoperazone (77%) followed by amikacin (66%) and even higher generation antibiotics such as meropenem (64%) and imipenem (61%). But sensitivity was not tested against tigecycline and colistin. Smolyakov R *et al* [17] and Towner KJ [18] studies were also showing *Acinetobacter* spp were resistant to aminoglycosides, cephalosporins and quinolones.

In our study we observed that *Pseudomonas aeruginosa* was highly sensitive to colistin, more resistant to aztreonam (63.6%) and cefepime (62.1%). A study conducted by Haeili M *et al* [15] showed that *Pseudomonas aeruginosa* was more susceptible to polymixin b (89.2%), ceftriaxone/tazobactam (89.2%) and piperacillin-tazobactam (80.3%), resistant to fluoroquinolones and even to higher generation antibiotics such as imipenem.

Escherichia coli was totally sensitive to colistin, tigecycline followed by cefoperazone-sulbactum (84.6%) and highly resistant to aztreonam, ampicillin, amoxicillin-clavulanate and cefuroxime (100%). The study conducted by Alquarshi A M [10] showed *Escherichia coli* was highly sensitive to aztreonam and imipenem (100%) and resistant to both ampicillin and cefoxitin.

In our study MRSA was 100% sensitive to linezolid, tetracycline and cotrimoxazole and it was 100% resistant to cefazolin followed by erythromycin, cloxacillin, ciprofloxacin, amoxicillin-clavulanate and ampicillin (87.5%). Haeili M *et al* [15] and Gupta A *et al* [14] showed MRSA was 100% sensitive to linezolid and vancomycin and 100% resistance to amoxicillin-clavulanate and oxacillin.

Most of the Gram negative organisms were highly sensitive to colistin, tigecycline whereas Gram positive organisms, MRSA and MSSA were highly sensitive to linezolid, cotrimoxazole, tetracycline and vancomycin but sensitivity pattern of *Streptococcus pneumoniae* was quiet variant and highly sensitive to colistin and highly resistant to cotrimoxazole.

The mortality in nosocomial infectious patients is multifactorial and directly related to the severity of the underlying disease. The highest impact on mortality of nosocomial infection has been found in moderately severe ill patients, rather than mild or extremely severe ill patients [19-21]. Patients who are very mildly ill may recover independently even in the presence of infection, while those are very severely ill may die regardless of accurate antibiotic therapy. However, patients infected with certain microorganisms like *Pseudomonas aeruginosa* may not be able to improve even with adequate treatment and also due to the additional efficacy of these organisms in promoting inflammation and alterations in pathophysiology of lung parenchyma [22].

In our study we observed that most common organisms causing high mortality rate were *Pseudomonas aeruginosa (93%)* followed by MRSA (73%), *Acinetobacter* species (68%) and *Klebsiella pneumoniae* (68%) which was also observed from previous studies [22]. The study conducted by Edis EC *et al* [16] showed that the mortality associated with MDR *Acinetobacter* species was high and difficult to treat.

The most prevalent resistance among *Staphylococci* is the methicillin resistance which is the major concern at present [23]. About 50% of the morbidity due to infectious in ICUs can be attributed to MRSA which was demonstrated by a European study and other studies [24, 25].

The mortality rate caused by MRSA (73%) is nearly twice as that of MSSA (36%) and other studies were showing MRSA cause higher rate of mortality than MSSA [5]. The mortality rate caused by MRSA was 73% Vs 25% while comparing our study to that of Gupta A *et al* [14].

The sensitivity and resistance pattern of *Streptococcus pneumoniae*, *Haemophilus influenza, Enterobacter* species *and Burkholderia* species was not taken into the consideration as the number of isolates were less.

CONCLUSION

The inappropriate and inadequate use of antibiotics leads to the emergence of MDR strains, resulting high mortality rates in HAP patients, which is the major concern in treating HAP. Most commonly isolated organisms were *Klebisiella pneumonia, Acinetobacter* spp, *Pseudomonas aeruginosa* and MRSA are multidrug resistant strains, susceptible to very few antibiotics and their associated mortality rates were very high especially with *Pseudomonas aeruginosa* and MRSA. Infection control in hospital and evaluation of sensitivity and resistance pattern of isolated organisms helps in selecting the appropriate empirical antibiotic therapy, to reduce further emergence of MDR strains and decreases the morbidity, mortality and hospital cost.

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