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Original Research Article

Bacteriological Profile and Antibiogram of Gram Positive Nosocomial Isolates from Intensive Care Units with Special Reference to High Level Aminoglycoside Resistance in Enterococcus Species in a Tertiary Care Hospital of North Karnataka, India

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Abstract

Introduction: Nosocomial infection is an important factor in determining clinical outcomes among patients admitted in intensive care units. Previous studies on nosocomial infections in ICUs found that respiratory tract infections, blood stream infections, urinary tract infections and soft tissue infections are the common nosocomial infections in ICUs. These infections are more commonly caused by Gram negative isolates followed by *Staphylococcus aureus, CONS* and *Enterococcus* species. These organisms isolated are highly resistant to antibiotics. Presence of high level aminoglycoside resistance in these *Enterococcus* isolates makes the treatment combination of cell wall inhibitor and aminoglycoside ineffective. Early recognition of bacteria and appropriate antimicrobial therapy are essential for control of infection, preventing the morbidity and improving the quality of life.

Objectives: To find out the profile of Gram positive bacteria causing nosocomial infection in patients admitted in intensive care units. To know the antibiotic susceptibility pattern of Gram positive nosocomial isolates and determining High level aminoglycoside resistance (HLAR) among *Enterococcus* species isolated.

Materials and Methods: A total of 192 samples were taken from various clinical specimens. The organisms were identified by gram staining, cultural characteristics and a battery of biochemical tests. Drug susceptibility was performed on the isolates by Kirby Bauer's disk diffusion method. HLAR producing Enterococcus species were detected by high level gentamicin and streptomycin discs.

Results: A total of 202 organisms were isolated from 192 various clinical samples. Respiratory tract infection 76(39.6%) was the most common infection in Intensive care units .The number of Gram positive isolates was 60 (29.7%) .142 (70.3%) Gram negative organisms were isolated. The most common Gram positive cocci was *Staphylococcus aureus* 34 (16.8%). Highest occurrence of nosocomial infections was observed in CCU 52(27.1%) followed by ICCU 48 (25%). Among Gram positive cocci minumum resistance was seen against vancomycin (6.7%) followed by linezolid (10%) and cotrimoxazole (26.6%). HLAR was seen in 100% of the Enterococcus species

Conclusion: This study shows that Gram positive bacteria cause severe infections in intensive care units. The most common isolates among Gram positive organisms were *S.aureus* CONS and Enterococcus species. The isolates were resistant to most of the drugs. For Gram positive cocci the most effective antibiotics were vancomycin followed by linezolid and cotrimoxazole. High level aminoglycoside resistance (HLAR) was seen in all the Enterococcus species isolated .Appropriate antibiotic utilization in Intensive Care Units is essential not only in ensuring an optimal outcome but also in the prevention of multidrug resistant bacteria.

Introduction

An infection is considered as nosocomial infection or Healthcare-Associated Infection (HAI) if it occurs within 48 hours after hospitalization, or after 3 days of discharge or 30 days after operation. According to CDC (Centre for disease prevention and control) guidelines The National Nosocomial

Survillence System (NNIS) states that nosocomial infection occurs due to an adverse reaction to the presence of an infectious agent or toxin that was not presenting or incubating at the time of admission to the hospital.[1,2]

Nosocomial infection is an important factor in determining clinical outcomes among patients admitted in intensive care units. Critically ill patients in intensive care unit (ICU) are ten times more likely to acquire nosocomial infections than those in general wards.[2,3]

Studies on nosocomial infections in ICUs found that respiratory tract infections, blood stream infections, urinary tract infections and soft tissue infections are the common nosocomial infections in ICUs. Samples of urine, blood, pus, sputum and endotracheal secretions when evaluated had Gram negative isolates followed by *Staphylococcus aureus, Coagulase negative Staphylococcus* species and *Enterococcus* species.[4,5,6]

These organisms isolated are highly resistant to antibiotics. Most of them are methicillin resistant *Staphylococcus aureus*, high level aminoglycoside producing *Enterococci*, vancomycin resistant *Enterococci*, beta- Lactamase producing *Escherichia coli* and *Klebsiella* species & carbepenam resistant members of family *Enterobacteriaceae*.

For Gram positive isolates the most effective drug has been vancomycin. Imipenem has proved to be most effective against majority of the isolates and is as a reliable agent for empirical treatment of majority of the ICU isolates.[7,8,9]

Interventions to control spread of resistant bacteria causing nosocomial infections include optimization of antibiotic selection and dosing, strict adherence to infection control practices and rational use of antibiotic combinations. Antimicrobial sensitivity pattern in ICU are crucial and important for giving effective treatment and decreasing the spread of resistance. The incidence and prevalence of multidrug resistant organisms are so high in the hospital settings that even effective drugs like fluoroquinolones, third generation cephalosporins, aminoglycosides etc. are decreasing their utility in covering hospital pathogens, thus restricting the choice of antimicrobials for treating serious infections. Early recognition of bacteria and appropriate antimicrobial therapy are essential for controlling infection, preventing the morbidity and improving the quality of life.

Materials and Methods

1. Source of data

The present study was undertaken at the department of Microbiology, BLDEUs Shri B.M.Patil medical college and hospital, Vijayapur during the period from 01-01-2014 to 30-06-2015. The study included a total of 192 samples taken from patients of both sexes irrespective of age groups admitted in the ICUs of BLDEUs ,Shri B.M. Patil medical college, hospital and research centre, Vijayapur.

Inclusion Criteria

Samples collected after 48 hours of admission of the patient to neonatal ICU(NICU), surgical ICU (SICU), pediatric ICU (PICU), Intensive cardiac care unit (ICCU) and critical care unit (CCU were included. Single or mixed growth from patients were included in the study.

Exclusion Criteria

Anaerobic, fungal organisms, repeat samples from the same patient and samples collected before 48 hours of admission of the patient to ICU were excluded.

2. Ethical considerations

The study was reviewed and approved by institutional ethical committee, BLDEUs Shri B.M. Patil medical college, hospital and research centre, Vijayapur.

3. Specimen collection and transport

The specimens collected were blood, urine, pus and respiratory samples like sputum, endotracheal secretion and throat swab.

4. Processing

Gram staining was done by using Modified Hucker's method. Gram Positive cocci and Gram negative bacilli were seen. The samples were inoculated on Nutrient agar, Blood agar and Mac Conkey's medium for samples other than urine. Urine samples were inoculated on CLED agar and Mac Conkey's medium. The media were incubated at 37°C for 24-48 hours. Organisms were identified by various biochemical tests.

Antibiotic susceptibility tests was done on Gram positive isolates by Kirby bauer disc diffusion method according to CLSI guidelines (2012) [10]. Penicillin (10µg) cloxacillin (10µg), ciprofloxacin (5µg), cefuroxime (30µg), ceftriaxone (30µg), cephalexin (30µg), azithromycin (15µg), gentamicin (10µg), tetracycline(30µg), linezolid (30µg), vancomycin (30µg). norfloxacin (10µg), piperacillin-tazobactam (100/10µg) and cotrimoxazole (25µg) discs were used.

Detection of HLAR in Enterococcus isolates[11]

Method: Disc diffusion method

Procedure

High level aminoglycoside resistance was detected by using high concentration gentamicin (HLG

120µg) and streptomycin (HLS 300µg) discs. The discs were applied to the MHA plate swabbed with the test strain adjusted to 0.5 McFarland turbidity standard and incubated at 35°C for 24 hours.

Interpretation

Organisms were deemed HLAR producing when zone of inhibition was ≤6 for HLG and ≤6 for HLS discs.

Statistical analysis

It was carried out by SPSS 14 software and data was analysed

1. In the form of percentage with tables
2. By diagrammatic presentation in the form of pie charts and graphs
3. The association was calculated by Chi-square test - P value ≤ 0.05 was considered as Significant.

Results

A total of 202 organisms were isolated from 192 various clinical samples. Most of the isolates were from respiratory specimens [sputum 38, endotracheal secretion 32 and throat swab 6] 76 (39.5%) followed by pus samples 44 (22.9%), urine 40 (20.8%), blood 32 (16.7%).(Table -1)

Table 1: Distribution of various clinical samples received from different ICUs

Specimen	No	Percentage (%)
Respiratory specimens	76	39.5%
1. Sputum 38 (19.8%)		
2. ET secretion 32(16.7%)		
3. Throat swab 06(3.1%)		
Pus	44	22.9 %
Urine	40	20.8 %
Blood	32	16.7%
Total	192	100%

Most of the samples obtained were from males 116 (60.6%) and 76 (39.6%) were from females. Respiratory tract infection 76(39.6%) was the most common infection in Intensive care units. It was followed by skin and soft tissue infection 44 (22.9%), urinary tract infection 40 (20.8%) and blood stream infection 32 (16.7%).(Fig 1)

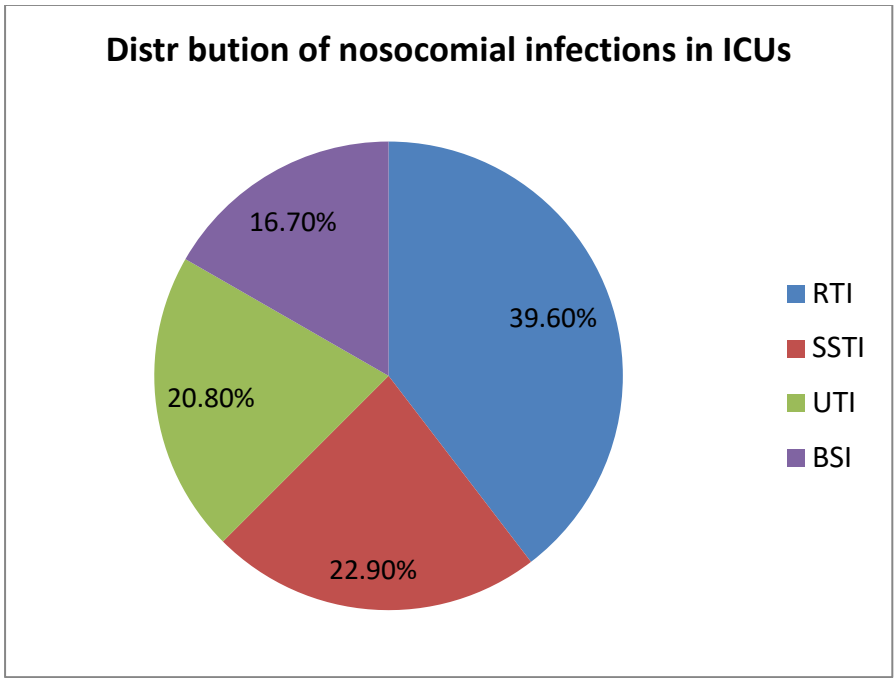

Figure 1: Distribution of nosocomial infections in ICUs

Out of the 192 samples processed 202 organisms were isolated. From 182 samples single organism was isolated. 10 samples had mixed growth. The number of Gram positive isolates was 60 (29.7%). 142(70.3%) Gram negative organisms were isolated. Statistically there was a significant difference between the isolated number of Gram positive cocci and Gram negative bacilli.(p value < 0.001) (Table 2)

Table 2: Bacteriological profile of Gram positive organisms causing nosocomial infections in ICUs

Organisms	No	Percentage (%)
Gram positive cocci (60)		
1.Staphylococcus aureus	34	16.8%
2.CONS	16	7.9%
3.Enterococcus species	10	4.9%

Highest occurrence of nosocomial infections was observed in CCU 52(27.1%) followed by ICCU 48 (25%). (Fig 2)

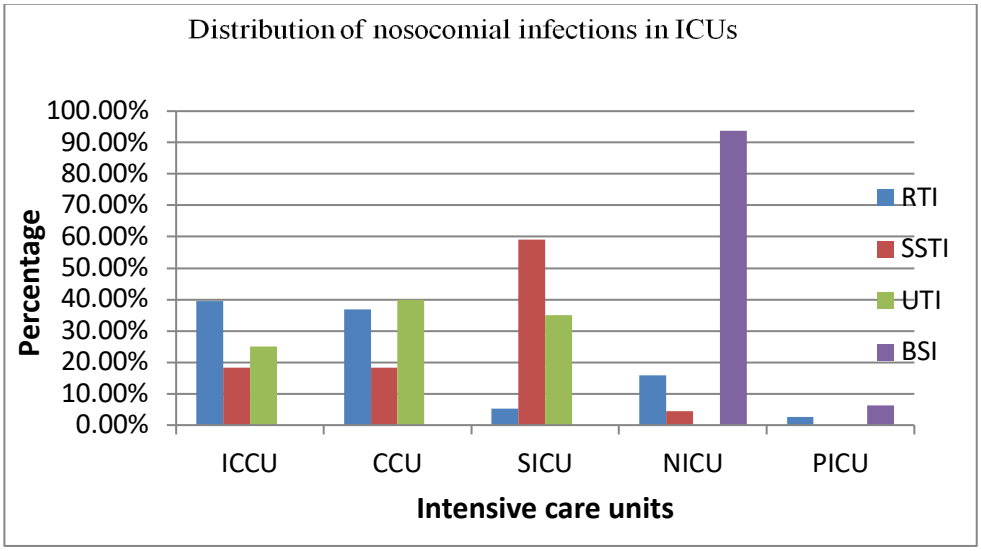

Figure 2: Distribution of nosocomial infections in different ICUs

The sensitivity pattern of Gram positive organisms causing nosocomial infections in ICUs is given below. Maximum resistance was seen against penicillin and norfloxacin (96.6%) followed by cephalexin (93.3%) and ceftriaxone, ciprofloxacin (83.3%). Minumum resistance was seen against vancomycin (6.7%) followed by linezolid (10%) and cotrimoxazole (26.6%). (Fig 3) All of the *Staphylococcus aureus* were seen to be resistant against penicillin (100%). It was followed by resistance to cephalexin and norfloxacin (94.1%). High resistance was also seen against cloxacillin and ceftriaxone (82.3%), ciprofloxacin and cefuroxime (76.5%) and, azithromycin and gentamicin (58.8%). Maximum susceptibility of *Staphylococcus* was seen against vancomycin (100%) followed by linezolid (94.1%), cotrimoxazole (88.2%) and tetracycline (70.6%). The resistance pattern of *S, aureus* for different types of antimicrobial agent is statistically significant (p value < 0.0001). Among CONS .

maximum resistance was seen against fluoroquinolones like ciprofloxacin and norfloxacin (100%) followed by penicillin (87.5%) and cephalosporins. Most of them were found to be susceptible to vancomycin (100%) followed by linezolid (87.5%), cotrimoxazole and tetracycline (62.5%). The resistance pattern of CONS for different types of antimicrobial agents is statistically significant (p value < 0.0001).

Most of the *Enterococcus* species were found to be resistant to penicillin, cloxacillin, cephalosporins, azithromicin, gentamicin and norfloxacin (100%) followed by tetracycline, piperacillin – tazobactam (80%) and cotrimoxazole (60%). Maximum susceptibility was seen against linezolid (80%) followed by vancomycin (60%). The resistance pattern of Enterococcus species for different types of antimicrobial agents is statistically significant (p value < 0.0001).

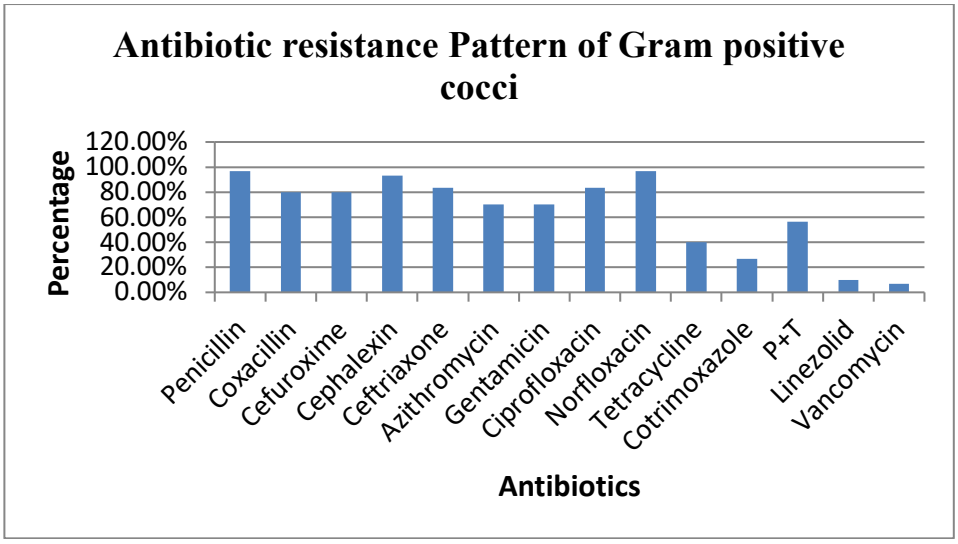

Figure 3: Antibiotic resistance pattern of Gram positive cocci

Distribution of HLAR showing Enterococcus species

High level aminoglycoside resistance was seen in 10(100%) of *Enterococcus* species. 40% of HLAR showing *Enterococcus* species were responsible for SSTI and UTI. Blood stream infection was caused by 20% of HLAR showing *Enterococci.*(Fig 4). 40% of *Enterococcus* species caused infection in ICCU. Infections in SICU, NICU and CCU was caused by 20% of Enterococcus species.(Fig 5).

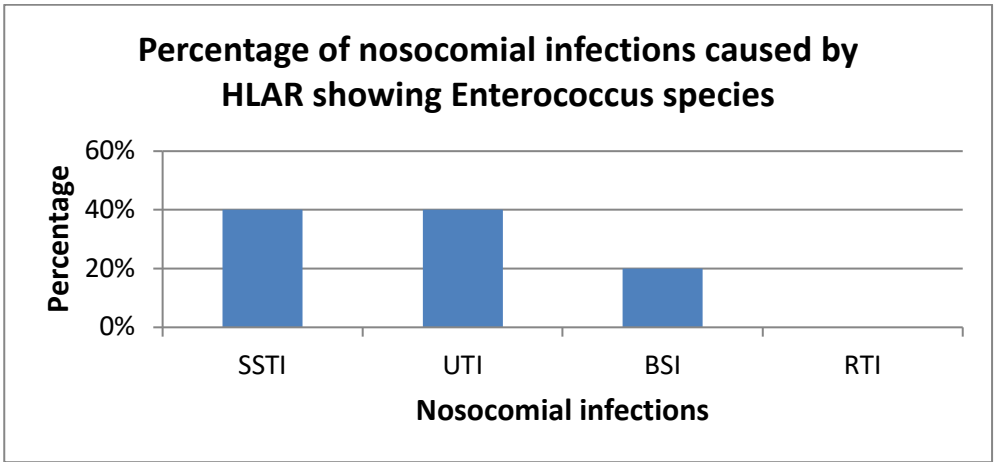

Figure 4: Percentage of nosocomial infections caused by HLAR showing *Enterococcus* species

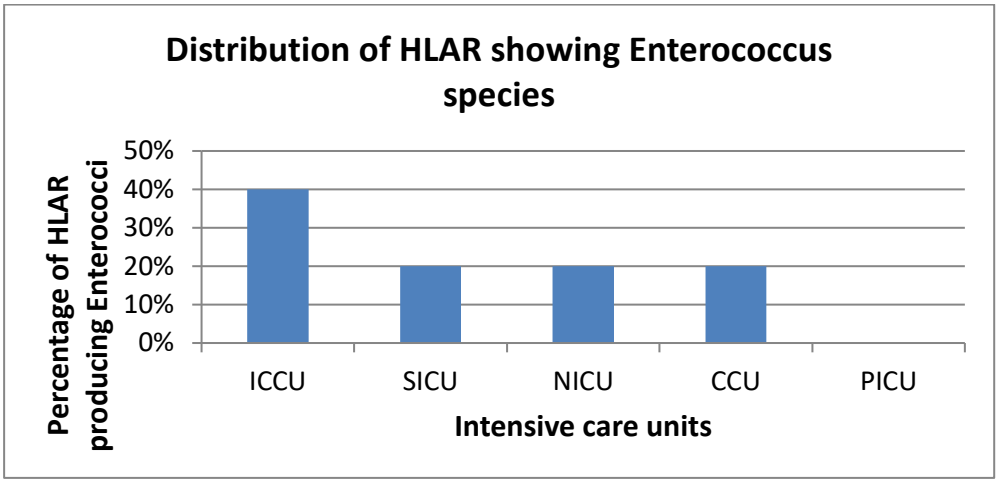

Figure 5: Distribution of HLAR showing *Enterococcus* species in different ICUs

Discussion

Nosocomial bacterial infections are a major cause of morbidity in hospitalised patients. Patients in the intensive care units (ICUs) have higher risk of nosocomial infections compared with the average patients.20-25% of the nosocomial infections develop in ICUs. A large number of bacteria like *S.aureus, CONS, Enterococcus species like E.faecalis and E.faecium, Klebsiella pneumoniae, E.coli, Citrobacter freundii, Pseudomonas aeruginosa* and *Acinetobacter baumannii* are potential pathogens in hospitalised patients which can lead to respiratory tract infections, urinary tract infections, skin and soft tissue infections and blood stream infections.[12]

Antibiotic resistance in the intensive care units (ICUs) is a major worldwide problem. It has been found that the spread of drug resistant organisms in the ICUs is due to the widespread use of antibiotics. The rate of resistance in the ICUs is several fold higher than the general hospital setting.

Distribution of various clinical samples received from different ICUs

In this study a total of 202 organisms were isolated from 192 various clinical samples. Most of the isolates were from respiratory samples 76 (39.5%) [sputum 38 (19.8%), endotracheal secretion 32 (16.7%) and throat swab 6 (3.12%)] followed by pus samples 44 (22.9%), urine 40 (20.8%) and blood 32 (16.7%). Our data corelates with the results of study conducted by Zhanel GG *et al*. [13] However in the results published by Sharma SK *et al*[14] respiratory specimens were the most common followed by urine and blood. Another report by Patel BV *et al* [6] highlights the variability in distribution of specimens where most of the isolates were from urine samples followed by blood and pus. The widespread use of tracheal intubation and mechanical ventilation to support the patients in ICUs increases the risk of nosocomial respiratory tract infections. In the present study most of the samples obtained were from males 116 (60.6%) and 76 (39.6%) were from females. This is in consistence with the study conducted by Zhanel GG *et al* [13], Pradhan N *et al* [15] and Baghaei R *et al* [16] where most of the isolates were from male patients. It is in contrast with the study conducted by Al-Jawady ZA *et al* [2] where most of the isolates were obtained from females.

Nosocomial infections in Intensive care units are predominantly respiratory tract infections and in accordance with this, the most common nosocomial infection in the present study was respiratory tract infection 76(39.6%). It was followed by skin and soft tissue infection 44 (22.9%), urinary tract infection 40 (20.8%) and blood stream infection 32 (16.7%). The widespread use of mechanical ventilation and endotracheal intubation in critically ill patients increases the risk of nosocomial respiratory tract infections. Comparable results have been published by Gunseren F *et al* [12], Mathur P *et al* [17].

It is in contrast with the study conducted by Mythri H *et al* [18] where the most common nosocomial infection was urinary tract infection followed by respiratory tract infection.

In the present study out of the 192 samples processed 202 organisms were isolated. From 182 samples single organism was isolated. 10 samples had mixed growth. The number of Gram positive isolates was 60 (29.7%). 142 (70.3%) Gram negative organisms were isolated. This predominance of Gram negative bacteria is coincident with the finding of some recent studies (Zhanel GG *et al* [13], Mathur P *et al* [17], Patel BV *et al* [6], Al Jawady ZA *et al* [2].

Concerning the Gram positive cocci the most common isolate was *S. aureus 34* (16.8%) followed by Coagulase negative *Staphylococci* 16 (7.9%) and *Enterococcus* species 10 (4.9%). This is similar to the other previous studies [6,12,13,17]. The overall decrease in frequency of Gram positive cocci in comparison to Gram negative bacilli may be due to direction of empirical therapy towards the Gram positive one, in the time that the Gram negative bacteria show resistance to this therapy. [2]

In the present study highest occurrence of nosocomial infections was observed in CCU 52(27.1%) followed by ICCU 48 (25%). Majority of the respiratory tract infections were seen in ICCU 30 (39.5%), skin and soft tissue infections in SICU 26(59.1%), urinary tract infections in CCU 16 (40%). In CCU the most common nosocomial infection was urinary tract infection 16 (40%) This is similar to the study conducted by Dandagi GL19. All of critically ill patients used indwelling catheter, a device thought to be the most significant risk factor for developing nosocomial infections.[33]

In ICCU respiratory tract infection was the major infection 30 (39.5%) which is in accordance with the study conducted by conducted by Kucukates E *et al* [8] where the percentage of respiratory tract infection in ICCU was 50.3%. Mechanical ventilation, particularly prolonged coma or reduced conscious level, supine positioning, aspiration, pre-existing diseases like COPD, old age, malnutrition and use of nasogastric tubes are the predisposing factors for nosocomial respiratory tract infections. The organism may gain access into the lungs by one of the several routes like aspiration of oropharyngeal secretions, aspiration of gastric contents, inhalation, hematogenous spread and direct inoculation and exogenous penetration (eg: pleural space).[19]In SICU the major infection was

skin and soft tissue infection 26 (59.1%) which corelates with the study conducted by Iyer AP *et al* [20] where the most common infection was surgical wound infection (35.2%). During the dressing of wounds cross transmission occurs either by the hands of personnel or by contaminated instruments. Compromised membrane and skin barriers following the use of invasive devices can also lead to infections. On the other hand Bayram A *et al* [21] concluded in their study that the most common infection in SICU was respiratory tract infection (31.5%)

In the present study in NICU, highest occurrence of blood stream infections was seen 30 (93.7%). Risk factors include catheter insertion and care practices, products administered through the line, frequency of manipulation, age group, underlying disease, and severity of illness of the patient. In case of catheter induced infection, infection may occur as a result of migration of microorganisms from the insertion site along the percutaneous tract.[27] This data is in consistent with the study conducted in Canada.[22]

Antimicrobial agents are among the most commonly used drugs among hospitalised patients. The emergence of antimicrobial resistance in ICUs is of great concern as it increases the likehood of drug interactions / side effects and cost of therapy due to use of newer antibiotics. In the present study maximum resistance was seen against penicillin and norfloxacin (96.6%) followed by cephalexin (93.3%) and ceftriaxone, ciprofloxacin (83.3%). This high rate of resistance might be due to the selective influence of extensive usage of these drugs.

Minimum resistance was seen against vancomycin (6.7%) followed by linezolid (10%) and cotrimoxazole (26.6%). The high level of sensitivity may be due to less frequent use of such antibiotics in hospital. These data are comparable with the results by Al Jawady ZA *et al* [2], Datta P *et al* [3], Sheth KV *et al* [9] and Zhanel GG *et al* [13] where minimum resistance was seen against vancomycin and linezolid and maximum resistance was seen against beta lactam group of drugs like penicillin and cephalosporins. In the present study the resistance seen against fluoroquinolones like ciprofloxacin is similar with the study conducted by Al –Jawady *et al* [2] where it was seen to be (71.5%). but is in contrast with the study conducted by Sheth KV *et al* [13] where high sensitivity was seen (80%).

All the strains of *S.aureus* and CONS were found to be susceptible to vancomycin and linezolid followed by cotrimoxazole and tetracycline similar to previous studies.[3,13] This is in contrast with the study conducted by Sheth *KV et al* [9] where there was a high resistance seen against cotrimoxazole (75%) in *S.aureus*. Maximum resistance was seen against penicillin and cephalosporins followed by cloxacillin. High resistance was also seen against fluoroquinolones, azithromycin and gentamicin. It is similar to other studies. [2,3,9,13]

Distribution of HLAR showing Enterococcus species

HLAR (High level aminoglycoside resistance) is defined as resistance to gentamicin and streptomycin There is secretion of enzymes which inactivates the aminoglycoside by different mechanisms such as adenylation and phosphorylation. *Enterococci* are important nosocomial agents and serious infections caused by them are often treated with a combination of cell wall inhibitor and aminoglycoside. However the presence of high level aminoglycoside resistance in these isolates makes this treatment combination ineffective.[23] High level aminoglycoside resistance to high concentration gentamicin and streptomycin was seen in 10(100%) of *Enterococcus* species. This is similar to the study conducted by Mathur P *et al* [17] where 100% of the *Enterococcus* species showed high level amino glycoside resistance. This is also in accordance with the study conducted by Randhawa VS *et al* 79 where 68% of *Enterococcus* species had high level gentamicin resistance and 43% of *Enterococcus* species had high level streptomycin resistance.

40% of HLAR showing Enterococcus species were responsible for SSTI and UTI. Blood stream infection was caused by 20% of HLAR showing Enterococci.

Conclusion

Nosocomial infections in ICUs are foremost aspect that need to be tackeled carefully and efficiently by the healthcare professional for the betterment of patients who are hospitalized. The prescribing of antibiotics in ICUs is usually empiric. Therefore the ongoing surveillance of antibiotic susceptibility pattern of bacteria is fundamental effort to monitor changes in susceptibility patterns and guide the clinician in choosing empirical therapy appropriately. Appropriate antibiotic utilization in ICUs is crucial in ensuring optimal outcome and preventing emergence of multidrug resistance bacteria.

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