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Original Research Article

Study of utilization of antimicrobial drugs and its resistance pattern in patients with septicemia at a tertiary care hospital

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ABSTRACT

Background: Many types of bacteria can produce septicemia. The most common infections that lead to septicemia are urinary tract infections, pneumonia, nephritis and abdominal infections.
Methods: The study aims to assess the pattern of antimicrobial drugs used in septicemia and to assess the etiological organisms and their drug sensitivity and resistance pattern. Study participants admitted to tertiary health care centre and who are having septicemia were included in this prospective observational study. Blood culture, bronchial secretions were subjected to microbiological analysis. The etiological organisms, their drug sensitivity and resistance pattern and the outcome of drug therapy were recorded. The clinical course of the study participants was monitored till cure either the resolution of pneumonia. Qualitative data were analyzed using the chi-square test or Fischer's exact test and quantitative data using the independent t test.
Results: Mean duration of hospital stay in all patients 13.22±0.45 days and in resistance cases it was found 19.22±0.45 days. Mean duration of ICU stay in all patients was 4.34±0.45 days and in resistant cases mean duration of ICU stay was 8.18±0.45 days. Clinical outcome in overall admitted patients recovered was 97 patients (80.83%) death was 16 patients (13.33%). Clinical outcome in resistant patients recovered 16 patients (13.33%) and death 26 patients (21.66%).
Conclusions: The organisms had a varied sensitivity and resistance pattern. The clinical outcome was multifactorial.

Keywords: Antimicrobial drug resistance, Intensive care unit, *Pseudomonas*

INTRODUCTION

Septicemia occurs due to release of chemicals in bloodstream to fight an infection trigger inflammation. It produces series of changes that damage multiple organs, leading them to organ failure leading to death. Symptoms include fever, difficulty breathing, low blood pressure, fast heart rate and mental confusion.[1]

Studies indicates that septicemia accounts 1.7 million United states adults per annum and responsible for contributing 250 000 deaths. Various studies estimate that septicemia is present in 30-50% of hospitalizations that culminate in death.[2]

INDICAP study analyzed 4038 patient data and reported a prevalence of severe sepsis of 28.3% out of which 20.5% were ICU acquired.[1] This is a much lower prevalence than described in point prevalence study (INDICAP) conducted in 120 ICUs across India. INDICAP study analyzed 4038 patient data and reported a prevalence of severe sepsis of 28.3% out of which 20.5% were ICU acquired.

Studies conducted by Sharmila et al found that 6% of all ICU admission was due to severe sepsis out of which 16% were ICU acquired.[3]

Sepsis is a major cause of morbidity and mortality and the second leading cause of death worldwide. Epidemiologic

data on sepsis varies depending on the origin of database-community-based or hospital-based, nature of data collection-retrospective chart review, discharge diagnoses, diagnosis in death certificates, or prospective observational studies. A robust epidemiological study methodology should be prospective in nature conducted over a prolonged period and should include heterogeneous case mix representative of the disease, thus allowing generalizability of observed data. Epidemiological data on sepsis come mostly from western literature. Data from India are sparse and in the form of epidemiology of infection rather than sepsis which is a host response to infection. Moreover, literature and surveys conducted in India concentrate on microbiological profile, resistance pattern, antibiotic usage, ands outcome rather than sepsis epidemiology. This study was conducted a prospective observational study on severe sepsis for 5 years in a tertiary care hospital in India.[4]

Pneumonia refers to infection of the pulmonary parenchyma which accounts for 55.4% of deaths due to lower respiratory tract infections and 103 million loss of disability-adjusted life-year. Tracheal intubation and mechanical ventilation used to support the critically ill patients puts them at a greater risk of developing nosocomial infections. Nosocomial infections are infections that patients acquire either in the hospital or such facilities such as nursing homes, outpatient clinics, or diagnostic laboratories NIs are seen in 5-10% of hospitalized patients.

More than 60% of these infections are due to pneumonia, urinary tract infection, and bloodstream infection Microorganisms are resistant to one or more antimicrobials in 70% of these infections. Nosocomial pneumonia broadly includes ventilator-associated pneumonia (VAP), hospital-acquired pneumonia, and healthcare-associated pneumonia. Lung parenchymal infection which develops 48 h after mechanical ventilation (either endotracheal tube] or tracheostomy) is referred as VAP.[5] VAP is seen in 28% of patients who receive mechanical ventilation with a mortality rate of 48%. The most common pathogens causing VAP are bacteria including multidrug-resistant pathogens.[6]

The objectives of this study were to assess the pattern of antimicrobial drug use in septicemia and the etiological organisms involved, as well as their antimicrobial susceptibility.

METHODS

It is prospective randomized observational study. The study duration was eighteen months. The study was conducted at B. J. government medical college, Pune (Maharashtra) from March 2023 to October 2023. The institutional ethics committee approved the study. All study participants meeting the inclusion and exclusion criteria were included in the study after written informed consent.

Inclusion criteria

Subjects of either gender, aged ≥18 years admitted as inpatients in Kempegowda institute of medical sciences and hospital, Bengaluru, who received mechanical ventilation and developed VAP. Subjects willing to give a written informed consent.

Exclusion criteria

Subjects in whom adequate sputum samples cannot be obtained, subjects with viral, fungal, or aspiration pneumonia, subjects with tubercular (TB) pneumonia, subjects who are seropositive for HIV infection, subjects with diagnosed malignancy, subjects with pre-existing VAP were excluded and subjects and/or legal representative(s) not willing to give written informed consent.

The sample size was one hundred twenty (120) patients. Laboratory investigations including serum urea and creatinine, serum electrolytes, arterial blood gas analysis, and serum procalcitonin (in sepsis patients) were carried out. The specimen (bronchial secretions) obtained from all study subjects were subjected to microbiological analysis shows the various microbiological analysis performed in the bronchial secretions obtained. Drug therapy for septicemia was initiated empirically and was further adjusted according to the drug sensitivity and resistance pattern the demographic details, comorbid conditions, duration of hospital stay, and the drug therapy during the hospital stay, including antimicrobial drugs used were recorded. The pattern of antimicrobial use including the class of antimicrobial agents, formulation, dose, route, frequency, duration of administration, and any change in antimicrobial therapy were recorded. The etiological organisms, their drug sensitivity and resistance pattern, and the outcome of drug therapy were documented.

Improvement/worsening of the condition was clinically assessed also using repeat chest X-rays, blood counts, and other laboratory parameters. The clinical course of the study subject was monitored till either the pneumonia was resolved or the patient was discharged from the hospital or for 30 days, whichever was later. The outcome measures assessed were total duration of the patient stay in the hospital, total duration of patient stay in ICU and 30-day mortality.

Data was collected in Microsoft excel sheet using latest version of SPSS and analyzed by descriptive statistics and chi square test.

RESULTS

The patients were examined for demographic characteristics like gender, age group, occupation, education level, socioeconomic background and living status. Total patients included were 120 patients. In these groups 116 (58%) were male and 84 (42%) were female.

Age groups 18-30 years (22 patients), 31-40 years (34 patients), 41-50 years (28 patients), 51-60 years (31 patients), more than 60 years (5 patients). There was no statistically significant difference between the various age groups. Occupation of participant patients as per Kuppuswamy socioeconomic scale was skilled (40 patients), semi-skilled (30 patients), unskilled (30 patients), unemployed (20 patients). There was no statistically significant difference as per occupation groups. Participants education level was illiterate (60 patients), primary school (20 patients), high school (40 patients), graduate (10 patients), post graduate (10 patients) and there was no significant difference in the groups. Socioeconomic background lower (48 patients), middle (52 patients), upper (20 patients). The living status was rural (80 patients) and urban (60 patients).

Table 1: Demographic characteristics, (n=120).

Characteristics	N (%)	P value
Gender		
Male	70 (58)	0.58
Female	50 (42)	0.33
Age group (In years)		
18-30	22	0.56
31-40	34	0.89
41-50	28	0.54
51-60	31	0.43
>60	5	0.43
Occupation as per Kuppuswamy socioeconomic scale		
Skilled	40	0.45
Semi-skilled	30	0.56
Unskilled	30	0.43
Unemployed	20	0.32
Education level		
Illiterate	60	0.45
Primary school	20	0.67
High school	40	0.33
Graduate	10	0.23
Post graduate	10	0.12
Socioeconomic background		
Lower	48	0.56
Middle	52	0.45
Upper	20	0.78
Living status		
Rural	80	0.45
Urban	60	0.33

Risk factors for septicemia found was age >60 years, male gender, coma, ARDS, reintubation and neurosurgery, COPD.

Antimicrobials used at the time of ICU shift of patients were cephalosporins 45 patients (37.49%), macrolide 44 patients (36.66%), carbapenem 40 patients (33.33%), piperacillin + tazobactam 38 patients (31.66%), linezolid 36 patients (29.99%), vancomycin 34 patients (28.33%), levofloxacin 32 patients (26.66%), clindamycin 29 patients (24.16%), amikacin 27 patients (22.49%), gentamicin 20 patients (16.66%).

Table 2: Risk factors for septicemia.

Risk factor	N (%)
Age > 60 years	5 (6)
Male gender	70 (58)
Coma	3 (3.6)
ARDS	3 (3.6)
Reintubation	3 (3.6)
Neurosurgery	3 (3.6)
COPD	2 (2.4)

Table 3: Antimicrobials used at the time of ICU shift of patients.

Antimicrobials used	N (%)
Cephalosporins	45 (37.49)
Macrolide	44 (36.66)
Carbapenem	40 (33.33)
Piperacillin + Tazobactam	38 (31.66)
Linezolid	36 (29.99)
Vancomycin	34 (28.33)
Levofloxacin	32 (26.66)
Clindamycin	29 (24.16)
Amikacin	27 (22.49)
Gentamicin	20 (16.66)

Concomitant drug therapy observed was beta blockers 38 patients (31.66%), calcium channel blockers 36 patients (29.99%), magnesium sulphate 34 patients (28.33%), diuretics 12 patients (9.99%), levetricetam 11 patients (9.16%), phenytoin 10 patients (8.33%), rosuvastatin 8 patients (6.66%), insulin 6 patients (4.99%) and enoxaparin 6 patients (4.99%).

Table 4: Concomitant drug therapy.

Concomitant drug therapy	N (%)
Beta blockers	38 (31.66)
Calcium channel blockers	36 (29.99)
Magnesium sulphate	34 (28.33)
Diuretics	12 (9.99)
Levetricetam	11 (9.16)
Phenytoin	10 (8.33)
Rosuvastatin	8 (6.66)
Insulin	6 (4.99)
Enoxaparin	6 (4.99)

Change of antimicrobial agents was found from ceftriaxone to levofloxacin in 6 patients (4.99%), piperacillin + tazobactam to colistin and meropenem 6 patients (4.99%), cephalosporins to polymyxin B 4 patients (3.33%), macrolide to meropenem 3 patients (2.49%), carbapenem to meropenem 2 patients (1.66%), vancomycin to meropenem 1 patients (0.83%) and levofloxacin to colistin 1 patients (0.83%).

Table 5: Change of antimicrobial agents.

Previously used antimicrobials	Changed antimicrobials	N (%)
Ceftriaxone	Levofloxacin	6 (4.99)
Piperacillin + tazobactam	Colistin, meropenem	6 (4.99)
Cephalosporins	Polymyxin B	4 (3.33)
Macrolide	Meropenem	3 (2.49)
Carbapenem	Meropenem	2 (1.66)
Vancomycin	Meropenem	1 (0.83)
Levofloxacin	Colistin	1 (0.83)
Total		23 (19.16)

The mean duration of hospital stay in all patients was 13.22±0.45 days and in resistance cases it was found 19.22±0.45 days. The mean duration of ICU stay in all patients was 4.34±0.45 days and in resistant cases mean duration of ICU stay was 8.18±0.45 days.

Table 6: Comparison of mean period of stay in ICU and total hospital stay.

Parameters	Duration of hospital stay, days, mean ± SD	Duration of ICU stay days, mean ± SD	P value
All patients included	13.22±0.45	4.34±0.45	<0.01
Resistance cases	19.22±0.45	8.18±0.45	<0.01

Clinical outcome in overall admitted patients recovered was 97 patients (80.83%) while clinical outcome in resistant patients recovered 16 patients (13.33%).

Table 7: Clinical outcome in admitted patients.

Clinical outcome	Total cases, n (%)	Resistant cases, n (%)
Recovered	97 (80.83)	16 (13.33)
Death	23 (19.16)	26 (21.66)
Total	120 (100)	42 (34.99)

This prospective observational study on the pattern of antimicrobial susceptibility among organisms in septicemia and the pattern of antimicrobial drug use in the participants.

DISCUSSION

The risk factors for septicemia included age >60 years, male gender, coma, acute respiratory distress syndrome, reintubation, neurosurgery, chronic obstructive pulmonary disease (COPD), and thoracic surgery.[7,8] The purpose for ICU admission and mechanical ventilation in the study participants included acute respiratory failure, road traffic accident, congestive cardiac failure, cardiac arrest, shock, fulminant hepatic failure, and bacterial meningitis.[9] The common comorbidities seen in the study participants were type 2 diabetes mellitus, hypertension, liver dysfunction, renal dysfunction, ischemic heart disease and COPD. None of the WHO priority pathogens were encountered in this study.[10] The risk factors for septicemia, the reasons for ICU admission and mechanical ventilation and the comorbidities seen in the present study participants were akin to other reports by Karakuzu et al and Chittawatanarat et al.[11]

The antimicrobial agents that were used empirically in the study participants upon admission included cefotaxime, ceftriaxone, fixed drug combination of cefoperazone and sulbactam, azithromycin, clarithromycin, meropenem, FDC of piperacillin and tazobactam, linezolid, vancomycin, metronidazole, levofloxacin, clindamycin, and amikacin. This was also in consonance with a study by Tran et al.[12]

The organisms isolated from ICU endotracheal tube culture in the study participants with septicemia included *Acinetobacter*, *Enterococcus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* including coagulase negative *staphylococcus aureus*. The organisms isolated were akin to other observations by Restrepo et al. Saravanan and Raveendaran and Charles et al. The other Gram-positive organisms isolated in these studies were methicillin resistant *S. aureus* and *Streptococcus pneumoniae*, but in the present study, the gram-positive isolates were *S. aureus Enterococcus*.

The gram-positive isolates *S. aureus Enterococcus* were susceptible to clindamycin, erythromycin, and vancomycin and showed resistance to penicillin, amoxicillin cloxacillin combination and cefoxitin in studies reported by Ali et al and Golia et al. In the present study, the organisms were sensitive to cefepime, cefixime, levofloxacin, meropenem and vancomycin. Resistance was seen to amoxicillin + colxacillin combination, ampicillin, cefoperazone, cefoxitin, ceftriaxone, erythromycin, and clindamycin.

In the present study, *Acinetobacter* was sensitive to FDC of piperacillin and tazobactam, cefepime, cefixime, levofloxacin, azithromycin, clarithromycin, gentamicin, netilmicin, meropenem, polymyxin B, colistin and linezolid. They were resistant to FDC of amoxicillin and clavulanic acid, ampicillin, amikacin, tobramycin, ciprofloxacin, cotrimoxazole, and tetracycline. In a study done by Patil et al, *Acinetobacter* was sensitive to amikacin, colistin, meropenem, and tigecycline.[11] A study done by Joseph *et al.* showed resistance of *Acinetobacter* to ticarcillin, amikacin and ciprofloxacin.[13]

P. aeruginosa was sensitive to FDC of piperacillin and tazobactam, cefepime, cefexime, levofloxacin, gentamicin, netilmicin, meropenem, vancomycin and linezolid. They were resistant to FDC of amoxicillin and clavulanic acid, ampicillin, cefoperazone, cefoxitin,

ceftriaxone, ciprofloxacin, and amikacin. A similar resistance pattern was seen in the study by Joseph et al. According to a study done by Patil et al, these isolates showed sensitivity to amikacin, colistin, meropenem, and tigecycline.[14]

In the present study, *K. pneumoniae* was sensitive to FDC of piperacillin and tazobactam, cefepime, cefixime, levofloxacin, gentamicin, netilmicin, azithromycin, clarithromycin, polymyxin B, colistin, meropenem, vancomycin, and linezolid. This study was done in a tertiary care teaching hospital with infection control measures and a hospital antimicrobial use policy, which can be considered one of the major strengths of the study. This study describes the various organisms isolated from the endotracheal tube culture and their antimicrobial susceptibility along with the resistance pattern. This research had a small sample size and was carried out in a short duration, but the results can be used to frame and modify antimicrobial use policy and tighten infection control measures. Future studies done over a longer period involving a bigger sample size might show reveal new findings in terms of the pattern of antimicrobial susceptibility and resistance and organisms frequently involved in septicemia.

CONCLUSION

The antimicrobial agents given empirically were β-lactam antimicrobial agents, cephalosporins, macrolides, meropenem, metronidazole, amikacin, and linezolid. A change of antimicrobial agent was needed in 23 (19.16%) study participants based on the culture and sensitivity pattern of the organisms isolated. The organisms resistant to the empirical antimicrobial agents were commonly sensitive to linezolid, meropenem, vancomycin, polymyxin B, colistin, and levofloxacin. Resistance to FDC of amoxicillin and clavulanic acid, ampicillin, cefoperazone, cefoxitin, ceftriaxone, ciprofloxacin, erythromycin, amikacin, cotrimoxazole, and tetracycline was seen among the organisms isolated from endotracheal tube culture.

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