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Sepsis in Adults: Microbiological Agents and Antimicrobial Prescribing Patterns at BPKIHS

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Abstract: ***Background: As per Surviving Sepsis Campaign, early and empirical antibiotic treatment should be started in a patient suspected of severe bacterial infection. Many patients with sepsis remain in the emergency ward (EW) for several hours, the role of emergency physician in selecting appropriate antibiotics may be critical in lowering the mortality rate in patients with sepsis.[15,22,23] The goal of this study was to determine whether first line antibiotics selected by emergency physicians effectively covered disease causing organisms in patients presenting to EW with septic shock or severe sepsis. Materials and Methods: A cross sectional descriptive study was conducted for a period of one year from july 2013 to july 2014. All patients ≥16 years of age in EW with features of sepsis were included in the study. Samples were collected as per the standard protocol. The calculated sample size was "101". Data were entered in MS-EXCEL, converted to SPSS and analysed for different variables. Result: 421 cases were included, mean age was 36± 16.9 years with male:female = 1:2. Common sources of infection were urinary tract 45.84%, lungs and pleura 17.10%. Fever was most common (76.2%) complain in EW followed by cough (15.7%) and pain abdomen (12.4%). Overall culture positivity was 33.73%. Common isolated organisms were E. coli 35.91% and Staph. aureus 33.1%. Frequently prescribed antibiotics in EW were Ceftriaxone 70.5%, Metronidazole 42.7%, Piperacillin-Tazobactab 30.4%, Ciprofloxacin 21.4%. The susceptibility of ceftriaxone was maximum for against staph. 44% and <25% for rest of th6e organisms. Susceptibility of Amikacin was >85% for most of the organisms. The maximum susceptibility of ciprofloxacin was 50%. and that of vancomycin, tigecycline and linezolid is preserved to 100% in this study. Conclusion: There is high prevalence of multi drug resistant organism which leads to inappropriate empirical antibiotic prescription and associated increased mortality. So local susceptibility pattern should be reviewed periodically and accordingly protocol for empiric antibiotic prescription should be made in the EW for better outcome of patients of sepsis and septic shock.***

Keywords: Sepsis, Septic shock, antibiotic, susceptibility

1. Introduction

Bacteremia and sepsis are associated with an in-hospital fatality rate of 30-40%.[1] In the last two decades, bacterial infections have accounted for a higher percentage of fatality causes[2]. The Surviving Sepsis Campaign recommends initiating broad spectrum antibiotics targeted toward the source of infection within the first hour of recognition of septic shock[3].

Thus, early and empirical antibiotic treatment (i.e. given before the result of culture are available), in a patient suspected of harbouring a severe bacterial infection, is common wisdom. However, even putting to the best use all the data available within the hours of suspecting an infection, we are still left uncertain as to the pathogen and its susceptibility to antibiotics in the majority of cases. Many patients who have septic shock or severe sepsis remain in the emergency ward (EW) for several hours, the role of the emergency physician in rapidly selecting appropriate antibiotics for administration may be critical in lowering the mortality rate in patients diagnosed with septic shock or severe sepsis[4].

The goal of the study was to determine whether first line antibiotics selected by emergency physicians effectively covered disease causing organisms in patients presenting to the EW with septic shock or severe sepsis.

Some reports[5], but not all[6], show a significant reduction in fatality associated with appropriate empirical antibiotic treatment.

2. Materials and Methods

This prospective cross sectional descriptive study was carried out from july 2013 to july 2014 at Emergency ward (EW) of B. P Koirala Institute of Health Sciences (BPKIHS), Dharan, a tertiary care hospital in Eastern Nepal. All patients ≥16 years of age presenting in Emergency ward with features of sepsis i.e. who met the criteria of SIRS with suspected or definite focus of infection were included in the study. Patients or guardians not giving consent were excluded from the study

- All the samples required for this study was collected as per standard protocol for sample collection[7,8] before antimicrobial therapy.
- Sample size was calculated as 101 culture positive cases, assuming sensitivity of prescribed antibiotics being effective in the culture report as 80%[9] Specificity of chances of no antibiotics use in non sepsis patient as 50% Power as 80% and Confidence interval as 95%.

SIRS[10,11]**:** ≥2 of following.

1) Fever (oral temperature >38°C/100.4°F) or hypothermia (<36°C/96.8°F);
2) Tachypnea (>24 breaths/min) or P_aCO_2 <32mmHg;
3) Tachycardia (heart rate >90 beats/min);

4) Leukocytosis (>12,000/µL), leucopenia (<4,000/µL), or >10% bands; may have a noninfectious etiology.

Sepsis:-
1) SIRS that has a proven or suspected microbial etiology[10].

Severe sepsis[10]:
Sepsis with one or more signs of organ dysfunction

Septic shock[3,12]:-
Sepsis with hypotension (arterial blood pressure <90 mmHg systolic, MAP <65 or 40 mmHg less than patient's normal blood pressure) for at least 1 hr despite adequate fluid resuscitation.

Appropriate antibiotic: It was defined as the isolated bacteria being susceptible to at least one of the antimicrobials empirically administered as the first dose or 24 hours later[13].

Statistical Analysis
- Collected data was entered in Microsoft EXCEL and converted into SPSS 11.5 version and was analysed.
- For descriptive study proportion, percentage, mean, median and interquartile deviation were calculated and graphical and tabular presentation were made.
- For inferential statistics chi square (χ^2) test, independent t-test were applied to find out the significant difference between dependent and independent variable at 95% confidence interval, where p=0.05

Ethical consideration
Ethical clearance was taken from "Institutional Ethical review Board (IERB)" of BPKIHS.

3. Results

This cross sectional descriptive study comprised 421 cases. Mean (SD) age of patient at admission was 36± 16.9 years with a minimum age of 16 years old and maximum of 84 years. Male to female ratio of the patient was found to be 1:2. According to the stage of severity, 54% had sepsis syndrome, 28% severe sepsis and 18% septic shock. Sources of infection were urinary tract 45.84%, lungs and pleura 17.10%, post operative wound infection 10.68%, sepsis with MODS 7.36%, intra-abdominal 4.98%, others 14.0%.

Fever was the most common (76.2%) presenting complaint in the emergency room. Other complaints were cough(15.7%), pain abdomen(12.4%), discharge from surgical site(10.7%), burning micturition(14%), etc.

Overall culture positivity rate was 33.73% in the specimens of blood, urine, wound swab. Maximum positivity rate was found in wound swab culture where 70% positivity was found. A total of 11 different isolates were identified; Staphylococcus aureus, Klebsiella pneumoniae, Escherichia coli (E. coli), Acinetobacter spp., Enterococcus faecalis, Citrobacter koseri, Coag. Neg. Staphylococcus, Pseudomonas aeruginosa, Proteus, Pneumococcus, Enterobacter spp. Escherichia coli was the most common isolates (35.91%).

Single empiric antibiotic was used in 59 cases which constituted mainly ceftriaxone and in few ciprofloxacin, norfloxacin, azithromycin, ceftazidime. Two antimicrobial were used in 179 cases, frequently used combinations were ceftriaxone plus cefixime, ceftriaxone plus metronidazole, ceftriaxone plus amikacin, piperacilline-tazobactam plus metronidazole. Similarly three antimicrobial in 121 cases, four antimicrobial in 38 cases and five antimicrobial in 24 cases.

Table 3: Empiric antibiotic prescription pattern in emergency ward:

S.N.	Antibiotic	Used in no. of patients, N(%)
1	Ceftriaxone	297 (70.5%)
2	Metronidazole/Ornidazole	180 (42.7%)
3	Piperacillin-tazobactam	128 (30.4%)
4	Ciprofloxacin	90 (21.4%)
5	Levofloxacin	86 (20.4%)
6	Cefixime	76 (18%)
7	Amikacin	72 (17.1%)
8	Azithromycin	66 (15.7%)
9	Vancomycin	38 (9%)
10	Doxycycline	31 (7.4%)
11	Carbapenem	31 (7.4%)
12	Ofloxacin	21 (5%)
13	Aztreonam	17 (4%)
14	Teicoplanin	14 (3.3%)
15	Antifungal	4 (1%)
16	Others	107 (25.4%)

Table, shows most commonly used antimicrobials empirically were third generation cephalosporin (88%), quinolones (47%), imidazole group (42%) and Piperacilline-tazobactam (30.4%). Empirical antibiotics used in culture positive cases:

Amikacin was used in 4 cases each of staph. aureus and K. pneumonae, and five cases of Proteus. Ceftriaxone was used in 24 cases each of Staph. aureus and E. coli, 10 cases of K. pneumonae, 4 cases of Enterococcus fecalis and Pneumococcus, and 3 cases each of Pseudomonas and Proteus. Ciprofloxacin was given to 14 cases of E. coli, 7 of Staph. aureus, 4 cases for each of Enterococcus fecalis and Ptoteus, 2 and 1 for Pseudomonas and Enterobacter respectively. Vancomycin was given in 6 cases of pseudomonas, 4 of Acinetobacter, 2 each of Pneumococcus and Proteus, 1 case of enterobacter. Similarly Metronidazole was given to 24 cases of Staph. aureus, 7 cases of K. pneumonae, 5 cases of Pseudomonas, 4 cases for each of E. coli, Acinetobacter, Enterococcus, Citrobacter and CoNS.

Table: The culture specimen and agent identified:

Agent/Culture specimen	Staph. aureus	Klebsiella pneumoniae	E.coli	Acineto-bactersps.	Enterococcus spp.	Citrobacter koseri	Coagve Staph.	Enterobacter spp.	Proteus	Pseudo-monas	Pneu-mococcus	Total
urine	3	10	33	0	3	0	0	2	3	3	0	57
blood	28	0	0	4	4	0	0	0	0	5	3	44
wound swab	14	2	8	0	0	0	0	0	0	0	0	24

sputum	0	0	6	0	0	0	0	0	0	0	4	10
i.v. catheter tip	2	0	0	0	0	1	1	0	0	0	0	4
Stool	0	0	0	0	2	0	0	0	0	0	0	2
Drain fluid	0	0	2	0	0	0	0	0	0	0	0	2
CSF	0	0	2	0	0	0	0	0	0	0	0	2
Total	47	12	51	4	9	1	1	2	3	8	7	145

In this table, E.coli and Staph aureus were common organism identified. E. coli was more common in urine and wound swab and Staph aureus more common in blood and wound swab. Three culture results had two organisms.

Susceptibility pattern of Antimicrobial agents(AMA) against different microbes:

This study shows very good susceptibility of Amikacin against most of the microbes, 100% for each of E. coli and K. pneumonae, 86% for Staph. aureus, and about 70% for each of Proteus and Pseudomonas. Ceftriaxone has highest susceptibility for Staph. i.e 44%, about 20-30% for K. pneumonae, E. coli, Acenetobacter and Pneumococcus. Quinolones (Ciprofloxacin and Ofloxacin) have about 50% susceptibility against Staph., Enterobacter and Pseudomonas, and 25-30% against K. pneumonae and Acinetobacter. Nitrofurantoin has 100% susceptibility against Enterococcus fecalis and 75% against Klebsiella and E. coli and 50% against Staph. Vancomycin has 100% susceptibility against Staph., Enterococcus and Pneumococcus. Tigecyclin and Linezolid have 100% susceptibility against Staph. and Enterococcus. Imipenem has >80% susceptibility against Staph., Klebsiella, E. coli and Pseudomonas. Meropenem has 100% susceptibility against Citrobacter and Enterobacter, and 70-80% against E. coli and Pseudomonas.

Acinetobacter is resistent to most of the antibiotics but susceptible to Cotrimoxazole and Tobramycin. Citrobacter is 100% susceptible to Meropenem and Chloramphenicol. CoNS is 100% susceptible to Amikacin.

Outcome of patient with respect to appropriateness of empirical antibiotic used in culture positive cases:

Appropriate antibiotic was used in 29.6% of cases where mean hospital stay was 6 days with no deaths. Inappropriate antibiotic was used in 70.4% of cases where mean hospital stay was 8.7 days with 17 deaths. so it can be said that there is increasing trend of deaths and increased duration of hospital stay in inappropriate empiric antibiotic patients.

4. DISCUSSION

In this study, the ratio of male: female was found to be 1:2 but other studies show sepsis was more common in male[14-16]. This difference might be because in this study urinary system is the most common focus of infection and UTI is more common in female.

Most common focus of infection was found to be urinary system and next was respiratory system and then surgical site infection compared to respiratory tract being most common site of infection in other studies[16].

This study shows more deaths in patients administered different class combination therapy (DCCT) (β-lactams plus aminoglycosides, quinolones, or macrolides/clindamycin) whereas other studies shows increased survival of patients with the use of DCCT, this difference may be because of inappropriate selection of empiric antibiotic.

β-lactams, including carbapenems, are the most commonly used antibiotics in the critical care setting[14]. Similarly in this study too the most commonly used empirical antibiotic was β-lactam antibiotic (ceftriaxone) in 70.5%, next to it was imidazole antibiotics(42.7%), quinolones was used in about 21% of cases.

Many studies have demonstrated lower mortality and length of stay in patients with pneumococcal bacteremia or with community-acquired pneumonia receiving combination therapy, including a β-lactam plus a macrolide or a quinolone, than in those receiving monotherapy[14.]

Moreover, higher rates of side effects (mainly nephrotoxicity) were reported in the group of patients treated with β-lactam antibiotics plus aminoglycosides. A recent propensity-matched analysis concluded that, in patients with septic shock, the use of combination therapy with two or more antibiotics of different mechanistic classes was associated with lower mortality, shorter ICU stay, and lower in-hospital mortality[14]. But this study does not confirm these results of other studies may be because of above discussed reasons.

Nowadays, a great emphasis is being given on the hemodynamic aspects of sepsis in the ED[14] and the time taken for the administration of the first dose of an antibiotic as a major factor for the survival of patients with septic shock[15]. Less importance has been given to the possible benefit of an accurate initial empirical choice of antibiotics according to the suspected source of infection and to the local susceptibilities to antimicrobials. Appropriate antimicrobial therapy based on culture results was an important determinant of survival in a large cohort of patients with severe sepsis[14].

It may be argued that the antimicrobial use policy at any hospital should follow the knowledge of local antibiotic patterns of use and resistances. The clinical outcome of this fact is that the mortality rate of sepsis could be reduced with appropriate use of antibiotics[15]. This study highlights the very high rate of failure in selecting appropriate empirical antibiotic treatment in the ED.

The other cause of high rate of inappropriateness of empiric antibiotic could be possibility of high prevalence of ESBL-producing E.coli, as E. coli was most commonly isolated agent (35.9%) in the culture isolates of this study where carbapenem group would be more appropriate.

Acinetobacter spp., is a multidrug-resistant strain was found in four cases and significantly associated with inappropriate antimicrobial use. Therefore, risk factors for colonization or infection with multidrug-resistant strains of Acinetobacter spp. should be recognized, including ICU admission, previous colonization with methicillin resistant Staphylococcus aureus(MRSA), beta-lactamase inhibitor and carbapenem antibiotics use, bedridden status, previous intensive care admission, central venous catheter, surgery, mechanical ventilation, hemodialysis, and malignancy.[103] For infections caused by multidrug resistant Acinetobacter spp., antibiotic choices were usually limited. Options could be colistin[17] and tigecycline[17].

Therefore, risk factors for drug-resistant organisms as well as local patterns of antimicrobial susceptibility should be of top concern in selecting the empiric regimen[17].

5. Conclusion

This study showed sepsis is more common in female (68%). Most common focus of infection being urinary tract (46%) and lungs (17%). Most commonly used empiric antibiotic were ceftriaxone (70%), Imidazole group (42%). Most commonly used empiric combination were β-lactam + Imidazole and β-lactam + Quinolones 17% and 16% respectively. E.coli and Staph. aureus were most commonly isolated organisms 35% and 32% respectively. Among the tested antibiotics Vancomycin, Tigecycline and Linezolid have almost 100% of susceptibility. Ceftriaxone has about 25-30% susceptibility, Quinolone group has about 40-50% and aminoglycosides group has 85-100% susceptibility. The overall conclusion can be taken as there is high prevalence of multi drug resistant organism which leads to inappropriate empirical antibiotic prescription and associated increased mortality among this group of patient. So local susceptibility pattern of the microorganisms should be reviewed periodically and accordingly protocol for empiric antibiotic prescription should be made in the Emergency Ward for better outcome of patients both in terms of number of deaths and duration of hospital stay.

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