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Research Article

Study of the Resistance Pattern of Antimicrobials Used in Septicemia Patients in a Tertiary Care Teaching Hospital

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Abstract

Background: Globally, the development of Antimicrobial Resistance (AMR) in pathogen-causing infectious disease is a great public health concern, including our country, and is the main challenge for the physician. The present study was conducted to assess the current status of the resistance pattern of currently used antimicrobial agents in the setting of septicemia. **Method**: 384 Patients with Septicemia who met the study criteria, with Microorganism positive blood samples were included in this study. The study was conducted in Pt JNM Medical College Raipur and Dr. B.R.A.M. Hospital during the year of 2017-2019**).** It was a Prospective, Observational Study. **Result**: The majority of patients were newborn 210 (54.7%), Out of 384 patients, 244 were males (63.54%) and 140 were females (36.46%). In our study, the predominant bacteria isolated from blood Culture was Coagulase-Negative Staphylococcus (CONS) 139(36.2%), followed by *Klebsiella pneumoniae* 48 (12.5%). The Gram-positive and Gram-negative bacteria constituted 183(47.7 %) and 161(41.9%) respectively, Coagulase-negative staph aureus (CONS) was most sensitive to Vancomycin (89.2%) & high resistance to Ampicillin (88.5%), followed by Penicillin-G (86.33%). **Conclusion**: The current study showed that the most commonly affected population was neonates because of immaturity, low immune system development, and low birth weight. Our study showed an increase in resistance patterns to most of the commonly used antimicrobials. So judicious use of antimicrobials is recommended along with the regular update of Institutional antimicrobial policy according to the current pattern of antimicrobial sensitivity.

Keywords: Antimicrobial resistance (AMR); Septicemia; Coagulase-negative staph aureus (CONS); Antimicrobial sensitivity

Introduction

Paul Ehrlich described the antimicrobial agents as "MAGIC BULLETS" for killing the microbes but this impression of antimicrobial agents as magic bullets soon fell down after the discovery of penicillin by Alexander Fleming in 1928 who got the Nobel Prize in 1945. He warned that bacteria were capable to become resistant to antibiotics [1].

Globally, the development of antimicrobial resistance (AMR) in pathogen-causing infectious disease is a great public health concern, including our country, and is the main challenge for the physician. Because it leads to a prolonged hospital stay, morbidity, mortality and also increases the pharmacoeconomically burden of a country [2]. Antimicrobial resistance occurs when microorganisms (such as bacteria, fungi, viruses, and parasites) change their response to the exposed Antimicrobial drugs (such as Antibiotics, Antifungals, Antivirals, Antimalarials, and Anti-helminthic). Microorganisms that develop antimicrobial resistance are sometimes referred to as "superbugs" [2]. Septicemia or sepsis is a life-threatening condition that can lead to complications and death [3]. It occurs when the body responds to infection to its own tissues and organs, secondary to another site of infection.

The most common cause of septicemia is bacteria but may be caused by viruses, fungi, parasites, etc. Risk factors include both extremes of age, decreased immune response as in cancer,

diabetes, trauma, and burns. Common signs and symptoms are fever, increased heart rate and breathing rate, low blood pressure and confusion, etc. [4].

The spectrum of microorganisms associated with sepsis has changed from gram-negative organisms to gram-positive organisms since 1987. The incidence of fungal infections has increased from 1979 despite the introduction of various antifungal agents and mortality ranges from 41%-71% [5]. Worldwide, 13 million people develop sepsis each year, and as many as 4 million people have died [6]. The therapeutic management of sepsis, including septic shock, requires a comprehensive and systematic approach that includes a diagnostic method, the initiation of empirical antibiotic use, and the administration of supportive therapy [7]. Empirical antibiotic use is needed to eradicate the microbes that cause sepsis. Empirical antibiotic therapy must also consider the site of infection, the common pathogen that caused sepsis, and antibiotic sensitivity based on local patterns of antibiotic resistance [3].

According to the Center for Disease Control (CDC) AMR: is the ability of microbes to resist the effects of the drug so that germs are not killed, and their growth is not stopped [8]. Resistant microorganisms developed in the presence of antimicrobials because of misuse of drugs, irrational use of drugs and self-medication [9]. Resistance has emerged even to newer & more potent antimicrobial agents like vancomycin and carbapenem group of antimicrobials. So the Government of India has launched the "National Programme on containment of antimicrobial resistance under 12th five-year plan (2012-2017) [10].

Methods

Study design

It was a Prospective, observational study. This study was carried out over a period of 1 year from August 2017 to July 2018 in Department of Pharmacology and Department of Microbiology Pt JNM Medical College and Associated Dr. B.R. Ambedkar Memorial Hospital Raipur (C.G), Sample size -384 calculated by

$$n = z2 \times p \times (1 - p)/e2n = z2 \times p \times (1 - p)/e2$$ **where** (n=sample size, P=prevalence rate calculated from previous papers, e=error %, Z value-1.96 calculated from confidence interval of 95%**,** P=0.5, .e=5%.

Inclusion Criteria

1. Suspected septicemic inpatients whose blood samples were sent for culture sensitivity test and were positive for bacterial growth.
2. All age groups of patients were included in the study.

Exclusion Criteria

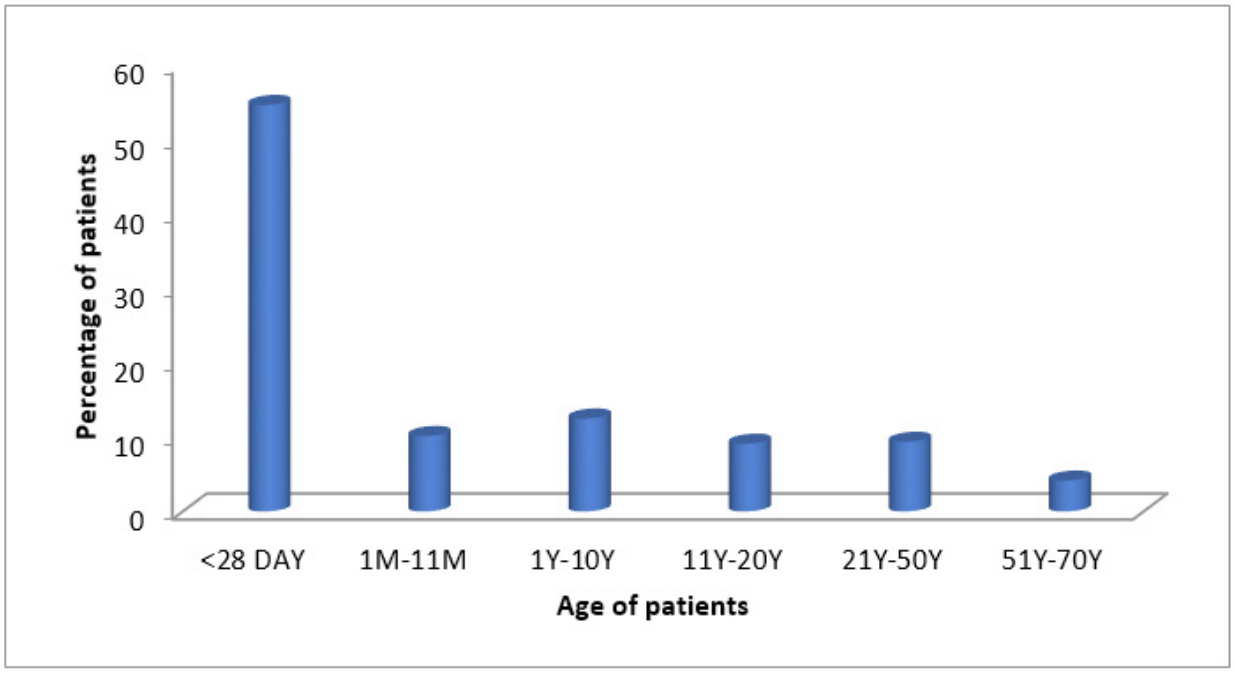
Patients whose blood samples did not show any growth.

Methodology

1. Study was conducted after obtaining clearance and approval from the institutional ethics committee. Patients were included in the study as per the inclusion criteria.
2. Written informed consent was obtained from all the study subjects / legal representatives for scrutinizing the records and collection of data after fully explaining the study procedure to their satisfaction.
3. A suitable case record form was designed to collect all necessary & relevant Information and details of antimicrobial agents used in empirical therapy were noted.
4. Culture & sensitivity test was done in a blood sample.
5. Sample Processing, identification of the organism, and antimicrobial sensitivity was carried out as per the clinical and laboratory standards institute guidelines [11].
6. Change in the therapy following the result of culture & sensitivity test was recorded and whether the change was in accordance with antimicrobial sensitivity pattern.
7. All data were tabulated and analyzed by MS excel 2007.

Results

384 patients of septicemia who met the study criteria, with micro-organism-positive blood samples were included in this study. Figure 1 summarizes the age distribution of the patients. The majority of patients were newborn 210 (54.7%), while 38 (9.9%) were found to be in age group 1month -11 months,49 (12.7%) patients were in the age group of 1 -10 years. 35 (9.1%) patients were in the age group of 11-20 years,36 (9.4%) patients were in the age group of 21-50 years. Minimum patients 16 (4.2%) were found between the age group of 51-70 years.



NOTE: M-month, Y-years

Figure 1: Age Distribution of the Patients.

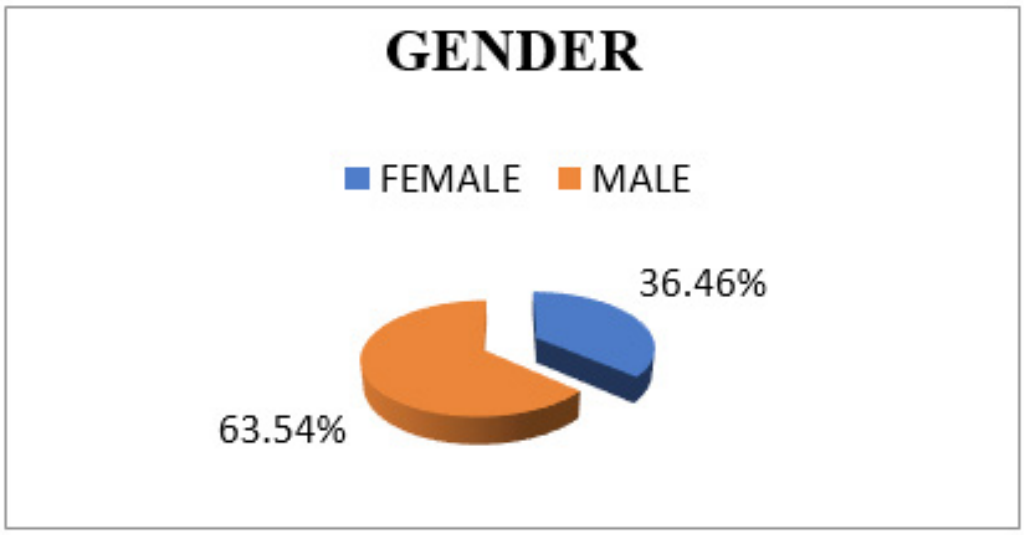
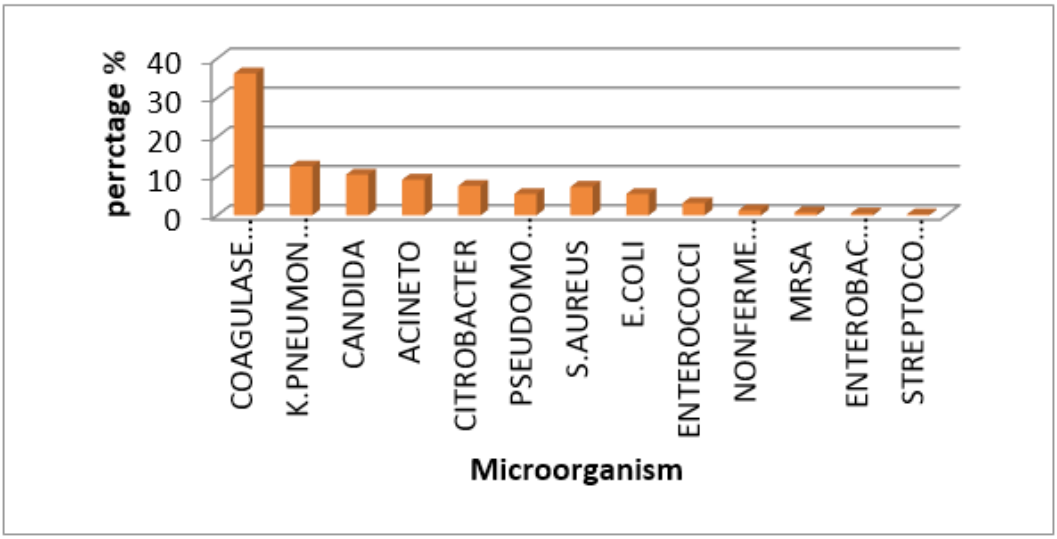


Figure 2: Gender distribution.

Out of 384 patients, 244 were males (63.54%) and 140 were females (36.46%). In our study the predominant bacteria isolated from blood culture was coagulase negative staphylococcus (CONS) 139(36.2%), followed by *Klebsiella pneumoniae* 48 (12.5%) , *Candida albicans* and non albicans 40 (10.4%), Acinetobacter 35(9.1%), Citrobacter 29 (7.5%), Pseudomonas 21 (5.5%), *Staphylococcus aureus* 28 (7.3%), E.coli 21(5.5), Enterococci 12 (3.1%), Non fermenter 5 (1.3%), Methicillin resistance *Staphylococcus aureus* (MRSA)3 (0.8%) ,Streptococci 1(0.3%) as shown in Figure 3.



Note: CONS-Coagulase negative *Staphylococcus aureus*

Figure 3: Common Microorganism Isolated from Blood Sample of Patients Antimicrobial Resistance Pattern of Gram-Positive Microorganisms.

Antimicrobial resistance patterns of Gram Positive and Gram -Negative microorganisms, causing septicemia were ranging from 20 to 100%. In our study Gram- positive Cocci, Coagulase Negative *Staph aureus* (CONS) was most sensitive to Vancomycin (89.2%), followed by cefotaxime (87.7%), Linezolid (87.5%), Amoxiclav (84.9%) whereas it showed high resistance to Ampicillin (88.5%), followed by Penicillin-G (86.33%), Cotrimoxazole (73%), Ciprofloxacin (53.83%), Gentamicin 41% and Ceftriaxone 25.89%. Piperacillin/Tazobactam was not tested (NT) against CONS (Figure 4).

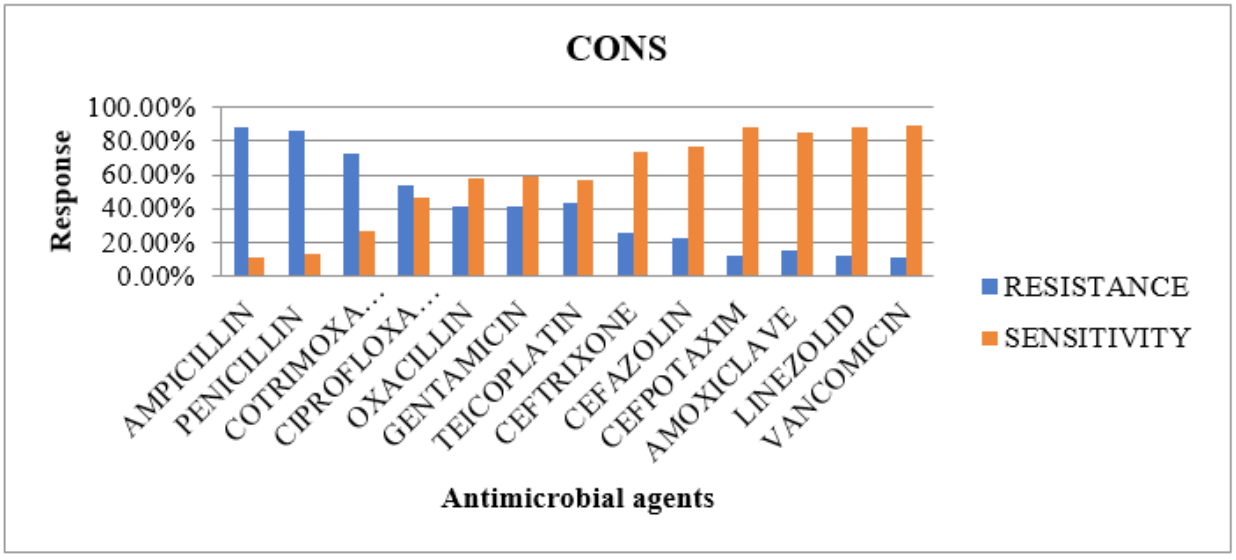


Figure 4: Response of Coagulase-Negative *Staphylococcus aureus* (CONS) to Various Antimicrobials

Commonly Prescribed Antimicrobial Empirically

Most of the patients belonged to the <1 year of age group and in that group Cefotaxime + Amikacin was the most commonly used drug (34.89%), followed by Piperacillin- Tazobactam + Amikacin (28.68%). Ceftriaxone was the third most commonly used antibiotic alone or in combination with Aminoglycoside. Meropenem, Imipenem, and Vancomycin were used as reserve drugs in the case of multidrug-resistant microorganisms. Others-include Ciprofloxacin, Gentamicin, Ampicillin, Metronidazole, CPM+AK –Cefotaxime + Amikacin, PIT+AK-Piperacillin -Tazobactam+ Amikacin. Change in the antimicrobial therapy after culture sensitivity test was seen in 89 patients (23.17%) whereas therapy was not changed in 295 patients (73.83%).

Discussion

In our study, 384 patients with septicemia were included who met the study criteria. The maximum incidence of septicemia was seen in extremes of age. In neonates (<28 day) the percentage of septicemia was 54.7%, followed by 12.7% between 1year to 10 years of age group. Similar findings were also reported by Meremikw MM, et al. [12], in which the majority of the patients were newborns (44.4%) and infants (21.0%). The incidence of neonatal sepsis is variable and differs from place to place, as it depends on various factors like gestational age, fetal birth weight, maternal nutrition, perinatal care, hygienic condition, and child health care facilities.

In the study, males were affected more than females and the male-female ratio was 1.74:1 which was similar to the study of Mustafa M, et al. in 2014 (1.58:1) [13] and Agnew M, et al. [14]. This finding is also in accordance with the study of Begum S, et al. [15] and Shrestha NJ, et al. [16]. The reason for male preponderance is unknown, but this could be due to sex-dependent factors [17]. The synthesis of gamma globulin is probably regulated by X-Linked immunoregulatory genes and as males are having one X chromosome compared to 2 X chromosomes, so they are more prone to sepsis than females [18].

Among the total cases, the most common pathogenic microorganism causing septicemia was gram-positive microorganisms (47.7%), followed by gram-negative microorganisms (41.9%) , and fungi (10.4%). This was similar to the study conducted by Jose Orsini, et al. [19] in which out of 122 isolates 72 (59%) were gram-positive bacteria, 38 (31.1%) were gram-negative organisms, and 12 (9.8%) were fungi. A similar result was also found in study conducted by Bhatnagar R, et al. [20] Udaipur Rajasthan in which out of 299 samples (37.37%), Gram-positive cocci accounted for 53.16%, Gram-negative for 46.50%, and Candida species as 0.33% of positive cultures.

In our study most frequently identified gram-positive bacteria was Coagulase-Negative *Staphylococcus aureus* (CONS) (36.2%). This was similar to the finding of Alam MS, et al. [21] in which the most frequently identified Gram-positive bacteria was Coagulase-Negative Staphylococci (CONS) 33 (63.5%). Similar results were also mentioned in the previous study by Dagnew M, et al. [14] and Orsini J, et al. [19]. The role of CONS in bacteremia is divisive. Until the 1970s, CONS were mainly recognized as a contaminant. Since then, several studies have reported increased incidence of infections due to CONS which is a skin commensal [22]. CONS are common microorganisms in nosocomial bacteremia due to the increase in medical device use including intravenous catheters, vascular grafts, prosthetic heart valves, and devices used in the treatment of joint disease. CONS are the most frequently isolated microorganisms from blood cultures. The presence of CONS in blood cultures cannot directly determine that the species is pathogenic, because in 85% isolate CONS were found as a contaminant [23,24].

Staphylococcus aureus (7.3%) was the second most common gram-positive isolates followed by Enterococci species (3.1%). Similar findings were also reported by a study conducted by Meremikwu MM, et al., Prabhu K, et al., Shah AJ, et al., Dagnew M, et al [12,14,25,26]. The resistance mechanism of CONS and Staphylococcus aureus occurs by movement of plasmid (contain resistance genes) from staphylococci as conjugation process [27].

Among gram-negative isolates, *Klebsiella pneumoniae* (12.5%) was the commonest microorganism isolated, followed by Acinetobacter (9.1%), Citrobacter (7.5%), Pseudomonas (5.5%) , *E. coli* (5.5%). Similar findings were also found in the study conducted by Pradipta IS, et al. [5]. Resistance to Gram-Negative bacilli occurs through three mechanisms by the production of enzymes that destroys antimicrobials like Beta-lactamase enzyme mutation of the antibiotic target, and by efflux pump [27].

In our study Fungi (*Candida albicans* and *Noncandida albicans*) was the third most common pathogenic microorganism (10.5%). In fungi, only a small percentage of the identified species cause disease in humans. Candida albicans species is responsible for an extremely large spectrum of disease [13]. Source of a candida infection can be endogenous (gastrointestinal flora or mucocutaneous colonization) or exogenous (hands of a health care worker, contaminated infusates) even leading to local outbreaks [14].

The antimicrobial resistance pattern of gram-positive microorganisms showed increased resistance to most of the antimicrobials routinely used. Among Gram-positive Cocci, Coagulase-Negative *Staphylococcus aureus* (CONS) was most sensitive to Vancomycin (89.2%), followed by Linezolid (87.5%), Amoxicillin-Clavulanic (84.9%) whereas it showed high resistance to Ampicillin (88.5%), followed by Penicillin-G (86.33%), Cotrimoxazole (73%), Ciprofloxacin (53.83%), Gentamicin 41%. A study conducted by Bhatnagar R, et al. [20] showed zero

percentage of resistance to Vancomycin and Linezolid. The emergence of the Glycopeptide resistance is of great concern. Though the first case of VRSA was reported in 2002 in the USA (Table 1).

Antimicrobial Agent	Klebsiella	Acinetobacter	Citrobacter	Pseudomonas	*E. coli*
	n=48	n=35	n=29	n=21	n=21
Ampicillin	41(85.41%)	30(85.71%)	24(82.75%)	20(96%)	21(100%)
Cefotaxime	32(66.66%)	25(71.42%)	22 (75.86%)	10 (48%)	19(90.5%)
Cotrimoxazole	25(52.04%)	22(62.85%)	14(48.27%)	NT	12(57.14%)
Piperacillin -Tazobactam	24 (50%)	17(48.57%)	12(41.37%)	10(48%)	NT
Amikacin	24(50%)	12(34.28%)	13(44.85%)	8(38%)	9(42.8%)
Cefixime	23(47.91%)	18(51.42%)	15(51.72%)	NT	14(66.7%)
Ceftriaxone	16(33.33%)	21(60%)	12(41.37%)	NT	19(90.5%)
Gentamicin	17(35.48%)	11(31.42%)	14(48.27%)	9 (42.85%)	10(47.9%)
Ciprofloxacin	15(31.25%)	16(45.71%)	18(62.06%)	17 (80.95%)	12(57.14%)
Imipenem	11(22.91%)	10(28.57%)	7(24.13%)	8 (38%)	3(14.28%)
Meropenem	13(27.09%)	7(20%)	6(20.68%)	7(33.33%)	2(9.5%)
Colistin	0(0%)	0(0%)	0 (0%)	0(0%)	2(9.5%)

Table 1: Antimicrobial Resistance Pattern of Common Gram Negative Microorganism.

In Gram-negative isolates, Klebsiella species (12.5%) were the most common microorganism found in our study and overall second most common etiological agent to cause sepsis. Klebsiella showed the most sensitivity towards colistin (100%) followed by Imipenem (77.09%), Meropenem (72.91%) whereas it showed high resistance to Ampicillin (85.4%), followed by Cefotaxime (66.66%), Cotrimoxazole (54.04%), Piperacillin- Tazobactam combination (50%). In the previous study conducted by Singh HH, et al. [28] in the (neonatal intensive care unit) NICU of our institute, Klebsiella was found to be highly sensitive to Meropenem (100%), Amikacin (85.71%), and Ciprofloxacin (81.43%).

In this study, most of the patients were neonates (<28 days of age) groups so prematurity was the most common predisposing factor of septicemia (26.82%), followed by LBW/VLBW/PTAFD (25%) (low birth weight, very low birth weight, Preterm appropriate for date). In addition to the specific microbial factors mentioned above, numerous host factors predispose the newborn to sepsis [29]. These factors are especially prominent in the premature infant and involve all levels of host defense, including cellular immunity, humoral immunity, and barrier function. Immature immune defenses, environmental and maternal factors contribute to the risk of neonatal sepsis, morbidity, and mortality, particularly in preterm and/or very low birth weight (VLBW) infants [16,29]. There may also be a genetic association [16].

Bloodstream infection (13.8%), Respiratory tract infection (12.8%), Fever of unknown origin (5.02%), Gastrointestinal Tract infection (GIT) (3.02%), skin infection (0.50%), and others (1.56%) were common sources of infection. Most of the patients belonged to <1 year of age group and in this age group third generation Cephalosporin in combination with Aminoglycosides (Cefotaxime + Amikacin) was most commonly prescribed drugs (34.89%) for empirical treatment of septicemia as per local antimicrobial susceptibility guidelines, followed by Piperacillin-Tazobactam combination (28.68%), Ceftriaxone was the third most commonly used antimicrobial agent alone or in combination with an aminoglycoside. Meropenem, Imipenem, and Vancomycin were used in the case of multidrug-resistant microorganisms as reserve drug [30].

In our study, we found that after the treatment of septicemia with susceptible antimicrobials around 75% of the patients responded to treatment, 19% of the patient died and 6% - leave against medical advice. This indicates that there are higher rates of mortality with septicemia although prompt empirical treatment was given. So besides the time to time surveillance of antimicrobial susceptibility patterns, other measures for the prevention of septicemia should also be applied, as proper hygiene should maintain in ICU settings.

Conclusion and Recommendation

Our study showed an increase in resistance patterns to most of the commonly used antimicrobials. So In the view of above findings, judicious use of antimicrobials is recommended. The institutional antimicrobial policy should be updated regularly according to the current pattern of antimicrobial sensitivity.

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