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Emerging Resistance in Cases of Septicemia with Special Reference to Vancomycin

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Abstract

Introduction: Blood Stream Infections increase the mortality rate, prolonging hospital stay in ICU, posing a challenge to the skill of not only the clinician but also to the microbiologist. Easy availability and indiscriminate use of antibiotics is leading to antimicrobial resistance. *Objective:* To review the spectrum of organisms isolated and their antibiotic sensitivity pattern in the Intensive Care Unit to minimize the risk of morbidity and mortality. *Method:* 235 suspected cases of septicemia from ICU were taken; co morbid illness and outcome were noted. Blood culture and their antibiotic susceptibility profile were done. *Results:* Of the 235 suspected cases, 47 (20%) were culture positive with Gram Negative Organisms predominant (70.21%) over Gram Positive Organism (27.65%). Klebsiella species was the most common organism isolated (38.29%). Of the 13 GPC, 38.46% cases showed Vancomycin resistance. *Conclusion:* Gram Negative Organisms were most common etiological agents with Klebsiella being most predominant. The rate of Vancomycin resistance from isolated organisms was high. Mortality rate was high (17.02%).

Keywords: Septicemia; Intensive Care Unit; Mortality; Vancomycin; Klebsiella.

Introduction

Septicemia is a systemic disease in which bacteria multiply within the blood and their toxic products causes harm to the host producing an infection [1]. It is a life threatening condition with resultant morbidity and mortality among hospitalized patients especially Intensive Care Units [2,3]. ICU creates an environment for infection because of the debilitating effect of the prolonged hospitalization as well as usage of various invasive medical equipments like airways and catheters [4]. The mortality rate of 90% associated with septicemia has declined to 24 – 58% after antibiotics have come into use, still keeping the burden of the disease on the higher end [5].

The non – specific presentation of symptoms of the disease, paves way for delayed treatment entailing risk of preventable mortality and sometimes leading to over treatment [6]. Though Gram Negative Bacteria, Gram Positive Bacteria and Fungi have been isolated from blood, the pattern of predominance varies from place to place, and even in the same place over time. The susceptibility to various antibiotics also varies with an increasing trend of developing resistance to higher antibiotics, resulting in major clinical crisis [7].

Bacteriological monitoring rises to the need of the hour to overcome this crisis of changing patterns [8]. Manual technique of Blood Culture takes a longer duration for isolation of pathogen, hence, automated blood culture systems like BacT/ALERT have significantly reduced the time for isolation allowing the clinician to reach to a judgment with ease [3,9]. The outcome of patients with sepsis is determined by the institution of early empirical therapy which is justified because of the severity of septicemia. But the initiation of specific therapy based on the microbiologist's antibiogram will improve the therapeutic outcome for efficient management of

the patients [3,10]. Testing and surveillance is not only required for therapy but also to monitor the emergence and spread of Multidrug Resistant organisms in order to amend the infection control practices if required.

The present study was conducted to review the spectrum of organisms isolated and their antibiotic sensitivity pattern in the Intensive Care Unit to minimize the risk of morbidity and mortality, besides reducing emergence of multidrug resistant organisms by rational antibiotic use for better patient care.

Materials and Methods

The present study is a prospective cross sectional study carried out from September 2015 to September 2016 over a period of 1 year in the Department of Emergency Medicine, Narayana Medical College, Nellore. Ethical Committee clearance was obtained from Institutional Ethical Committee of Narayana Medical College, Nellore.

A total of 235 suspected cases of septicemia admitted in Intensive Care Unit of Narayana Medical College were included in the study. After obtaining consent from patient or care givers, detailed history was taken and the co morbid illness like Respiratory conditions, Renal Cardiovascular, GIT conditions, Diabetes mellitus, Hypertension, Age > 65years, Surgery, Trauma, Poisonings, Snake bites, Cellulitis, Ulcers were noted down.

Proposed venipuncture sites were cleaned with 70% alcohol and Povidone iodine. 2 blood samples of 6–10 ml were collected from 2 different sites. The blood culture bottles were incubated at 37^0C aerobically in BacT/ALERT. Gram stain preliminary report was obtained from the positive samples. Plating was done on Blood agar, Nutrient agar, MacConkey's agar, Chocolate agar and incubated at 37^0C aerobically for 18–24hours. Growth was identified by standard biochemical reactions and presumptive identification of organism was made. Antibiotic susceptibility Testing was done by Kirby – Bauer Disc Diffusion Test method on Mueller Hinton Agar by Lawn culture method and reported as sensitive or resistant.

The antibiotics used were according to CLSI guidelines. The antibiotic discs used for Enterobacteriaceae were Ampicillin, Cefepime, Ceftriaxone, Cotrimoxazole, Ciprofloxacin, Amikacin, Gentamicin, Amoxicillin + Clavulanic acid, Cefoperazone + Sulbactam, Piperacillin + Tazobactam, Imipenem, Aztreonam, Colistin. The antibiotics used for Non fermenters were Ceftazidime, Cefipime, Ceftriaxone, Cotrimoxazole, Ciprofloxacin, Amikacin, Gentamicin, Cefoperazone + Sulbactam, Piperacillin+Tazobactam, Meropenem, Aztreonam.

The antibiotics used for Gram Positive Bacteria were Ampicillin, Oxacillin, Cefixime, Azithromycin, Ofloxacin, Amikacin, Tigecycline, Vancomycin, Clindamycin, Amoxicillin + Clavulanic acid, Piperacillin + Tazobactam, Linezolid, Teicoplanin and Daptomycin.

Results

Table 1: Number of Culture Positives

	Number	Percentage (%)
Culture Positive	47	20
Culture Negative	188	80
Total	235	100

Table 2: Gender wise Distribution of Culture Positive Cases

Gender	Number	Percentage (%)
Male	38	82.97
Female	9	19.14
Total	47	100

Table 3: Distribution of Organism

	Number	Percentage (%)
Gram Positive COCCI	13	27.65
Gram Negative Bacilli	33	70.21
Fungi	1	2.12
Total	47	100

Table 4: Organism Wise Distribution

Organism	Number	Percentage (%)
Gram Negative Bacilli		
Klebsiella pneumoniae	18	38.29
Pseudomonas aeruginosa	7	14.89
Acinetobacter species	4	8.51
Citrobacter species	2	4.25
Escherichia coli	1	2.12
Enterobacter species	1	2.12
Gram Positive COCCI		
Staphylococcus aureus	9	19.14
CONS	2	4.25
Enterococcus species	2	4.25
Fungi		
Candida	1	2.12
Total	47	100

Table 5: Age Wise Distribution

Age group (in years)	Number	Percentage (%)
11 – 20	3	6.38
21 – 30	6	12.76
31 – 40	11	23.40
41 – 50	12	25.53
51 – 60	7	14.89
61 – 70	4	8.51
71 – 80	1	2.12
81 – 90	3	6.38

Table 6: Outcome of the disease

Outcome	Number	Percentage (%)
Discharged	39	82.97
Death	8	17.02
Total	47	100

Table 7: Screening criteria in Culture Positive Patients

Criteria	Number	Percentage (%)
Hyperthermia	47	100
Tachycardia	47	100
Tachypnoea	47	100
Leukocytosis	43	91.48
Leukopenia	4	8.51

Table 8: Comorbid conditions among culture positive patients

Predisposing factor	Number	Percentage (%)
Respiratory condition	16	34.04
Hypertension	12	25.53
Diabetes mellitus	10	21.27
Surgery	8	17.02
Poisoning/ Snake bite/ scorpion sting	8	17.02
Renal Disease	7	14.89
Age >65years	6	12.76
Trauma	6	12.76
Cardiovascular Disease	4	8.51
GIT condition	4	8.51
Cellulitis / ulcers	4	8.51
Encephalitis	1	2.12

Table 9: Antibiogram of Gram Positive Bacteria

S. No	Antibiotic	Staphylococcus aureus (n=9)		CONS (n=2)		Enterococcus (n=2)	
		S (%)	R (%)	S (%)	R (%)	S (%)	R (%)
1	Ampicillin	0 (0)	9 (100)	0 (0)	2 (100)	0 (0)	2 (100)
2	Oxacillin	0 (0)	9 (100)	0 (0)	2 (100)	-	-
3	Cefixime	0 (0)	9 (100)	0 (0)	2 (100)	-	-
4	Azithromycin	0 (0)	9 (100)	0 (0)	2 (100)	0 (0)	2 (100)
5	Tigecycline	-	-	-	-	0 (0)	2 (100)
6	Amikacin	7 (77.77)	2 (22.23)	2 (100)	0 (0)	-	-
7	Vancomycin	6 (66.67)	3 (33.33)	2 (100)	0 (0)	0 (0)	2 (100)
8	Clindamycin	6 (66.67)	3 (33.33)	2 (100)	0 (0)	0 (0)	2 (100)
9	Amoxicillin + Clavulanic acid	0 (0)	9 (100)	0 (0)	2 (100)	1 (50)	1 (50)
10	Piperacillin + Tazobactam	0 (0)	9 (100)	0 (0)	2 (100)	2 (100)	0 (0)
11	Linezolid	8 (88.89)	1 (11.11)	2 (100)	0 (0)	2 (100)	0 (0)
12	Teicoplanin	5 (55.56)	4 (44.44)	2 (100)	0 (0)	2 (100)	0 (0)
13	Daptomycin	5 (55.56)	4 (44.44)	1 (50)	1 (50)	-	-

Table 10: Antibiogram of Gram Negative Bacteria

S. No.	Antibiotic	Klebsiella (n=18)		Citrobacter (n=2)		E.coli (n=1)		Enterobacter (n=1)	
		S (%)	R (%)	S (%)	R (%)	S (%)	R (%)	S (%)	R (%)
1	Ampicillin	0 (0)	18 (100)	0 (0)	2 (100)	0 (0)	1 (100)	0 (0)	1 (100)
2	Cefipime	1 (5.56)	17 (94.44)	0 (0)	2 (100)	0 (0)	1 (100)	1 (100)	0 (0)
3	Cotrimoxazole	1 (5.56)	17 (94.44)	0 (0)	2 (100)	0 (0)	1 (100)	0 (0)	1 (100)
4	Ciprofloxacin	7 (38.89)	11 (61.11)	1 (50)	1 (50)	1 (100)	0 (0)	1 (100)	0 (0)
5	Amikacin	8 (44.45)	10 (55.55)	2 (100)	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)
6	Gentamicin	2 (11.11)	16 (88.89)	0 (0)	2 (100)	1 (100)	0 (0)	0 (0)	1 (100)
7	Ceftriaxone	1 (5.56)	17 (94.44)	0 (0)	2 (100)	0 (0)	1 (100)	1 (100)	0 (0)
8	Amoxicillin + Clavulanic acid	0 (0)	18 (100)	0 (0)	2 (100)	0 (0)	1 (100)	0 (0)	1 (100)
9	Cefaperazone + Sulbactam	7 (38.89)	11 (61.11)	1 (50)	1 (50)	0 (0)	1 (100)	0 (0)	1 (100)
10	Piperacillin + Tazobactum	11 (61.11)	7 (38.89)	1 (50)	1 (50)	1 (100)	0 (0)	0 (0)	1 (100)
11	Imipenem	17 (94.44)	1 (5.56)	2 (100)	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)
12	Aztreonam	6 (33.33)	12 (66.67)	0 (50)	2 (100)	0 (0)	1 (100)	0 (0)	1 (100)
13	Colistin	17 (94.44)	1 (5.56)	2 (100)	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)

Table 11: Antibiogram of Non – Fermenters

S. No	Antibiotic	Pseudomonas (n=7)		Acinetobacter (n=4)	
		S (%)	R (%)	S (%)	R (%)
1	Ampicillin	0 (0)	7 (100)	0 (0)	4 (100)
2	Ceftazidime	0 (0)	7 (100)	1 (25)	3 (75)
3	Cefipime	3 (42.85)	4 (57.14)	1 (25)	3 (75)
4	Cotrimoxazole	0 (0)	7 (100)	1 (25)	3 (75)
5	Ciprofloxacin	6 (85.71)	1 (14.29)	4 (100)	0 (0)
6	Amikacin	6 (85.71)	1 (14.29)	4 (100)	0 (0)
7	Cefoperazone + Sulbactam	1 (14.28)	6 (85.71)	1 (25)	3 (75)
8	Piperacillin + Tazobactam	5 (71.42)	2 (28.57)	2 (50)	2 (50)
9	Meropenem	7 (100)	0 (0)	3 (75)	1 (25)
10	Colistin	7 (100)	0 (0)	4 (100)	0 (0)

Discussion

A total of 235 clinically suspected cases of septicemia were selected for the study. Out of all the blood samples processed, 47 cases were blood culture positive with a percentage of 20%. In studies conducted by P. Shreshta et al. [11] and Nalini Agnihotri et al. [12], 20% & 19.9% culture positivity were observed which is almost same as our study. Similar rates of septicemia were observed by Murthy et al. [10] (24.30%) and O.C Kingsley et al. [3] (23.4%).

Low Septicemic rates were reported by I. Starakis et al. [2] (15.1%) and Tarai B et al. [9] (13.70%). Higher rates were reported by Mahapatra et al. [13] (40%), K. J. Desai et al. [5] (46.20%) and I. Roy et al. [8] (47.5%). This wide range of septicemia rates by blood cultures can be due to difference in the volume collected, type of blood culture medium, automated blood culture systems as observed by Tarai et al. [9] in their study.

With respect to gender, there was a male preponderance for septicemia (82.97%) over female (19.14%). Such male predominance was observed in studies done by O. C Kingsley et al. [3] (52.17%), Vinay B. S. et al. [14] (66.6%) in contrast to higher rates in females as reported by Jung et al. [15] (Females – 65.75%).

Out of 235 cases in our study, 47 confirmed septicemia by culture, of which, Gram Negative organisms were 33 (70.21%), Gram Positive Cocci were 13 (27.65%) and 1 fungal isolate being Candida (2.12%) with Gram Negative organisms being predominant isolates. Studies done by B. Tarai et al. [9], K.J. Desai et al. [5] and Rahul Kamble et al. [16] reported Gram Negative organisms as predominant isolates causing septicemia with rates similar to our study as 78.22%, 67.85% and 69.01% respectively. Chaarakh et al[17] reported Gram Negative Bacilli too as predominant organisms but with higher isolation rates of 84.2%. In contrary, Gram Positive cocci were predominant isolates in studies by Starakis et al. [2] (58.5%), Edmond et al. [18] (64%) and Kingsley et al. [3] (62.7%).

Low fungal isolation was reported by Starakis et al. [2] (3%), K. J. Desai et al. [5] (3.57%) and S. Gandhi et al. [7] (2.43%) similar to our findings.

The most common isolate was Klebsiella species, 18 (38.29%), followed by Staphylococcus aureus, 9 (19.14%) with Pseudomonas aeruginosa 7 (14.89%) being 3rd most common organism. The predominance of Klebsiella isolates is correlated with studies by Murthy et al. [10] (26.9%), Chaarakh et al. [17] (46.8%) and Desai et al. [5] (47.14%). The higher Klebsiella septicemias might be due to number of ICU cases rising with increased sicker patients taken care of in the hospital as studied by A. M. Yinnon et al. [19].

Over the last few decades, Gram Positive Bacteremias are increasing accounting for the alteration in the isolates which is consistent with studies like those done by Kingsley et al. [3] (55.3%), Shreshta et al. [11] (38.8%) and Desai et al. [5] (25%), where Staphylococcus species were most commonly isolated similar to our study. The explanation to this might be the advancements in medical care, increasing virulence of Gram Positive isolates and abuse of Broad spectrum antibiotics as reported by Starakis et al. [2].

Low leukopenia rates of 8.5% were observed in our study. We have observed a mortality rate of 17.02% of the 47 patients, which is similar to that observed by Y. S. Igra et al. [20] (21%). Keeping this mortality rate in mind, appropriate antibiotics with life saving treatment is essential for a favourable outcome for the patient.

The common co morbid illnesses associated with septicemia were evaluated finding respiratory conditions (34.04%) being most common followed by Hypertension (25.53%), Diabetes mellitus (21.27%), surgeries like laprotomies (17.02%). Study conducted by Starakis et al. [2] found lower respiratory tract infection (39.1%) as the major risk factor followed by UTI (25.7%), Surgical site infections (7.2%) and Gastrointestinal infections (4.2%). Yinnon et al. [19] reported UTI (58%) as major risk factor where as Charles et al. [21] reported Diabetes mellitus (19.4%) and >65 years age (16.91%) as common risk factors.

Gram Positive Cocci (Staphylococcus and CONS) isolated in our study showed complete resistance to Ampicillin, Oxacillin, Cefixime, Azithromycin, Ofloxacin, Piperacillin + Tazobactam (100%) and higher resistance to Amoxycillin + Clavulanic acid (77.77%). Most of the isolates were sensitive to Linezolid (88.89%), Amikacin (77.77%), Vancomycin & Clindamycin (66.67%). We observed 55.56% isolates resistance for Teicoplanin and Daptomycin. Similar patterns were observed by Kingsley et al. [3] and Kumhar et al. [6] showing highest resistance to penicillins and lower resistance to amikacin and Vancomycin.

In terms to Enterococcus isolated among the septicemia cases, 100% resistance to ampicillin, Azithromycin, Tigecycline, Vancomycin, and Clindamycin was observed. Such high resistance rates to penicillins were observed by studies done by Kumhar et al. [6] and Edmond et al. [18]. High resistance to Vancomycin (44.8%) was reported by Starakis et al. [2]. Such high resistance rates might be attributed to the changes in the antimicrobial therapy for the empirical treatment of fever, lower cost and availability in the developing countries. Center for Disease Control and Prevention reports high level of Vancomycin Resistant Enterococci among patients in critical care units in 1980s and 1990s [23]. This study done now in the 21st century also displays resistant rates. To keep this in check, ongoing surveillance tracking upcoming resistant rates should be undertaken.

However, isolates being sensitive to Linezolid, Teicoplanin, Piperacillin + Tazobactam, provides the patients a relief to resort to high end antibiotics in critical and severe situations. It is surprising to note that Ceftriaxone and Amoxicillin + Clavulanic acid are displaying good activity against the Gram Positive Organisms in the era of Multidrug resistant Organisms.

Pseudomonas isolates have displayed complete resistance to Ampicillin, Cotrimoxazole, and 85.71% resistance to Ceftriaxone. Isolates were 100% sensitive to Meropenem and Colistin. The highest sensitivity to Carbapenems was observed in studies by O.C Kingsley et al. [3], Keerthi et al. [24](100%), Rahul Kamble et al. [16] (86.67%), and Shashi Gandhi et al. [7] (83.33%).

The antibiogram of Gram Negative Bacteria showed highest resistance to ampicillin, Amoxycillin + Clavulanic acid (100%), followed by Cefipime, Cotrimoxazole, Ceftriaxone (94.44%). 100% sensitivity is observed against colistin followed by imipenem (94.44%) correlating with other studies.

Conclusion

To conclude, our study has depicted Gram Negative Organisms most common etiological agents with Klebsiella being most predominant. Even though the rate of Gram positive organisms was considerably less than Gram Negative Organisms, the rate of Vancomycin resistance was high. We have observed a significantly high mortality rate indicating the severity of the condition. Implementation of Hospital

Infection Control practices like isolating patients harboring multi drug resistant organisms, curbing the usage of antimicrobials exerting selective pressure is extremely essential to save the patient from high costs and risks of prolonged hospital stay. Such regular surveillance with constant rapport and coordination between clinicians and microbiologists will ultimately provide patients with the best management of such a condition of high mortality.

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