Etiological Agent and Their Antibiotic Susceptibility Pattern Causing Adult Septicaemia in a Critically Ill Patients in a Tertiary Care Setting

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ABSTRACT

Objective: To determine bacterial profile in adult sepsis with their antimicrobial susceptibility pattern in our setup.

Study Design: Cross-sectional study.

Place and Duration of Study: Microbiology Department, Armed Forces Institute of Pathology, Rawalpindi Pakistan, from Dec 2018 to Dec 2019.

Methodology: Paired blood culture was collected in automated bottles and was processed as per standard protocol. The isolates were further identified and their susceptibility was performed according to Clinical and Laboratory Standards Institute (CLSI) 2019 guidelines.

Results: A total of 580 suspected septicaemia cases were taken into consideration. 169 (29.4%) were positive on blood cultures. Among culture-positive samples, Gram-negative bacilli (GNB) accounted for 113 (66.3%) isolates, while the remaining 56 (33.1%) were gram-positive isolates. Within gram-negative isolates, the most common species were 36 (31.8%) *Klebsiella pneumonia*, followed by 27 (23.8%) *Acinetobacter species* and 15 (13.2%) *Escherichia coli.* Multi-drug resistance (MDR) was observed in 98 (86.7%) isolates. Extended-spectrum beta-lactamase production (ESBL) was reported in 73 (64.6%) of enterobacterial. Among 56 Gram-positive bacterial isolates, 25 (44.6%) were *Methicillin-resistant Staphylococcus aureus* (MRSA), 23 (41%) were *Methicillin-resistant coagulase-negative Staphylococcus* (MR-CONS). Of the isolates, 8 (14%) were *Methicillin sensitive Staphylococcus aureus* (MSSA). None of the MR-CoNS and *S. aureus* strains was resistant to vancomycin.

Conclusion: Gram-negative bacilli outnumbered Gram-positive organisms in adult septicaemic patients. The majority of these organisms were multidrug-resistant, necessitating the need for timely culture and adjusting antimicrobials according to susceptibility profile.

Keywords: Adult septicaemia, Antimicrobial susceptibility, Blood culture, Multidrug resistance.

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INTRODUCTION

Bacterial sepsis constitutes a significant public health problem in developing countries and remains an important cause of morbidity and mortality in critically ill patients. The estimated fatality rate associated with bloodstream infection (BSI) is 15- 20% but reaches 35-50% in ICU patients. Approximately 200,000 cases of bloodstream infections occur every year, causing 20-50% mortality worldwide.[1] Respiratory tract, urogenital tract, and intra-abdominal infections are commonly identifiable primary foci of BSIs.[2] The impact of BSI has a tremendous impact on health care facilities by prolonging patient stay in the hospital and therefore in the intensive care unit, leading to increased health care costs.[3]

Sepsis is a fatal clinical syndrome caused by microbial invasion of normally sterile body parts. It is commonly defined as the presence of infection with the systemic inflammatory response syndrome (SIRS), leading to multi-organ damage, shock and ultimately death. It is characterised by the presence of two or more of the following parameters: (1) unusual body temperature (<36°C (96.8°F) or >38°C (100.4°F)); (2) heart rate >90 beats/min; (3) respiratory rate >20 breaths/min or partial pressure of carbon dioxide less than 32; and (4) white blood cell (WBC) count <4000/mm^3 or >12,000/mm^3.[4]

Elderly patients and patients with co-morbidities are more prone to sepsis; they often present with many symptoms, making it more challenging to make an early diagnosis and provide timely therapeutic management.[5]

The diagnosis of BSI can be confirmed by blood culture. A wide variety of bacteria has been isolated from the blood samples collected from critically ill patients. The most common include gram-negative bacteria such as *Escherichia coli, Pseudomonas aeroginosa, Klebsiella species, Enterobacter, Serratia, Citrobacter, Salmonella* and *Acinetobacter*.[6] However, a rapid rise in

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the trend of gram-positive isolates as a cause of sepsis have been observed over the period, possibly due to frequent use of invasive procedures and the increasing trends of hospital-acquired infection.[7] The timely diagnosis and rationale use of appropriate antibiotics remains the cornerstone in treating and managing patients with sepsis. However, frequent and irrational use of broad-spectrum antibiotics in critically ill patients who stay in the ICU for more pro-longed periods has increased bacterial resistance over time.[8] Antibiotics resistance is becoming an alarming problem in developing countries, including Pakistan. This leads to prolonged hospital stays and increased length of mechanical ventilation. Increasing antimicrobial resistance has become a global concern with economic and social implications worldwide.[9] In Pakistan, the unregulated over-the-counter sale of antibiotics, especially for self-treatment of infection in humans and to some extent for use in aniamals without prescription, has led to the rapid emergence of antimicrobial resistance. The prevalence of resistance among blood-borne bacterial isolates is increasing globally.[10] The rationale of our study was to analyse the etiologic agents of bacterial sepsis and to find out antimicrobial susceptibility patterns of bacteria isolated among critically ill adult patients.

METHODOLOGY

A cross-sectional study was conducted at the Microbiology department of Armed Forces Institute of Microbiology (AFIP), Rawalpindi Pakistan, from December 2018 to December 2019. Blood samples for culture and susceptibility testing were taken from all patients with clinical suspicion of septi-cemia admitted to adult surgical ICU and medical ICU of the Combined Military Hospital (CMH) Rawalpindi and Military Hospital Rawalpindi ICU of Armed For-ces Bone Marrow Transplant Centre (AFBMTC) Rawalpindi and liver transplant ICU (ALTU). The approval of the study was taken from Institutional Ethics Committee (FC-MIC-8/READ-IRB /18/669).

Inclusion Criteria: All the adult patients with suspected sepsis of either gender 18 years or above were included in the study.

Exclusion Criteria: Non-septic adult patients, patients who stayed in the ICU for less than 24 hours and HIV positive patients were excluded.

Informed consent was taken from all those patients included in this study, and their identity was kept confidential using a coding system. The sample size was calculated using the World health organisation (WHO) calculator taking blood culture positivity of 15.8%.[4] Non-probability consecutive sampling technique was used. About 10 ml of blood was drawn from two different peripheral sites under strict aseptic conditions in every patient. If the patient had a central venous line in place, then two samples were drawn from that line. Samples were then immediately put into designated blood culture bottles and sent to the microbiology department, then placed in their respected automated system. Positive samples, once flag positive, were then subcultured on 5% sheep blood agar and MacConkey agar. According to Clinical and Laboratory Standards Institute (CLSI) 2019 guidelines, the isolated organisms' antimicrobial susceptibility testing was performed by modifying Kirby-Bauer's disk diffusion method.[11] Minimum inhibitory concentrations of the antibiotics were obtained using the VITEK II system (BioMerieux, France). The double-disc synergy method performed extended-spectrum beta-lactamase (ESBL) testing. The susceptibility patterns of isolated pathogens to commonly used antimicrobials were then reported.

Documentation of variables like age, gender, and co-morbidities in patients whose blood samples were collected. Statistical Package for Social Sciences (SPSS) version 24.0 was used for the data analysis. Frequencies and percentages of the qualitative variables like gender, isolates and antibiotics were calculated. Mean, and standard deviation (SD) was calculated for numerical variables like age. The chi-square test was applied to find the association. The *p*-value lower than or up to 0.05 was considered as significant.

RESULTS

Out of 580 blood samples received from clinically suspected sepsis patients, 169 (29.4%) specimens were turned out to be culture positive. Among the culture-confirmed cases, 119 (70.4%) were male, while females were 50 (29.6%). The mean age of the patients was 43.9 ± 12 years (range from 18 to 76 years). 142 (84%) patients were treated successfully and discharged from the hospital after that. However, 27 (16%) patients died during their hospital stay (Table-I).

The frequency of isolates, their source of infection and co-morbidities were shown in the Table-II. The majority of the isolates causing gram-negative septicaemia 113/169 (66.3%) were from *Enterobacteriaceae* 69 (61%), while others were non- *Enterobacteriaceae* 44 (39%). There was a high prevalence of MDR 98(86.7%), and XDR isolates 15 (13.27%). Among gram-negative bacteria showing resistance to major groups of antibio-

tics that were commonly used as the first choice in empirical therapy, i-e, beta-lactam drugs, especially co-amoxiclav and third-generation cephalosporins, gentamycin, ciprofloxacin and tazobactam/piperacillin.

Table-I: Outcome of 169 septicaemic hospitalized patients.

Parameters		Outcome		*p*-value
		Treated 142 (84%)	Expired 27 (16%)	≤0.05
Gender				
Male	119 (70.4%)	101 (59.76%)	18 (10.6%)	<0.002
Female	50 (29.6%)	41 (24.26%)	9 (5.3%)	
Age Groups				
18-40	64 (38%)	61(36%)	3 (1.8%)	<0.002
41-76	05 (62%)	81(48%)	24 (14.2%)	

patterns plays a vital role in the management of BSI cases effectively.[12] Blood cultures remain the 'Gold standard' for diagnosing bloodstream infection. However, the rate of culture-positive cases varies worldwide on a geographical basis.[13] In our study, the overall prevalence of sepsis was 29%. Results of a similar study done in Pakistan (33%) and Ethiopia (28%)were in line with our results.[14] It was observed that a large number of patients whose blood samples were positive showed a high prevalence of other co-morbidities, like DM (58%), HTN (50.3%), CKD (41.4%), bronchial asthma/COPD (37.8%) and CVD (26.6%). The comparable results were also documented in another study done by Mayr *et al*,[15] which showed that severe sepsis is more likely in patients with a history of uncontrolled

Table-II: Frequency of isolates, primary source of infection and co- morbidities among culture proven cases (n=169)

Distribution of Isolates	Source of Infection	Co-Morbidities (More than 1)
Gram negative bacteria= 113 (66.3%) Gram positive bacteria= 56 (33.1%)	Respiratory system 58(34.3%) Urinary tract 28 (16.5%) Gastrointestinal tract 27 (16%) Multiple site infections 23 (13.6%) Skin and soft tissues 13(8%) Nervous system 12 (7.1%) Cardiovascular system 4 (2.3%) Unknown 4 (2.3%)	Diabetes mellitus = 98 (58%) Hypertension = 76 (45%) Renal failure = 69 (41%) COPD = 63 (37%) Hepatic failure = 39 (23.%) Haematological malignancy = 35 (20.7%)

Extended-spectrum beta-lactamase production (ESBL) was reported in 44/69 (64.6%) of *Enterobacteriaceae*, including 33/44 (75%) *Klebsiella pneumonia* and 11/44 (25%) of *Esherichia coli* cases. Carbapenem resistance (carbapenem-resistant organisms CRO) was detected in 38/101 (37.6%) gram-negative pathogens, including 14/38 (36.8%) *Klebsiella pneumonia*, 13/38 (34.2%) in *Acinetobacterbaumanii,* 3/38 (7.9%) *Esherichia coli*, 5/38 (13.1%) in Serratia marcescence and 2/38 (5.2%) in *Enterobacter cloacae isolates*. Three isolates of the total of 36 (8%) *Klebsiella pneumonae* and one isolate of the total of 27 *Acinetobacterbau-manii* (3.7%) showed resistance to polymixin, as shown in the Table-III. The antimicrobial susceptibility pattern of Gram-positive cocci was shown in the Table-IV.

DISCUSSION

Despite all the recent advances in medical care done so far, bacterial sepsis remains one of the leading causes of morbidity and mortality in developingcountries.[10] Incidence of sepsis varies from 13-39% in the different regions.[11] The etiological agents causing sepsis and their antimicrobial susceptibility are constantly evolving. Therefore, the study of bacteriological profiles with antimicrobial susceptibility

diabetes mellitus, chronic renal disease and chronic liver disease.

The overall spectrum of bacteria causing septicaemia has changed, Gram-negative bacilli being the most frequently isolated causative microorganisms than the gram-positive bacterias. Our study showed the same trend as 66.27% were Gram-negative bacilli while 33.1% were gram-positive isolates (*p*-value ≤0.05). Among these isolates, *Klebsiella spp.* (31.8%), was the predominant cause of sepsis in adults. The other leading organisms of septicaemia in our patients were *Acinetobacter spp.* (24%) followed by *E.coli* (13%) and Serratia marscence (8.8%). These findings were similar to a study conducted by Thomas *et al*.[16]

The commonest isolates cultured, *Klebsiella pneumonia*, expressed a multi-drug resistance pattern. These gram-negative bacilli showed >80% resistance to third and fourth generation cephalosporins and >40% resistance to carbapenems. A similar study done by Pal *et al*, reported 60% resistance to imipenem in the same organism.[17] Carbapenems are the 1st line treatment of ESBL producing Enterobacteriales. Wides-pread use of carbapenems in ICU settings contributes the most to this high level of resistance.

Table-III: Distribution of gram-negative bacterial isolates with their antibiotic resistance pattern from 169 culture-proven cases.

Gram Negative Isolates (n=113), (% Resistance to Antimicrobials)										
Antibiotics	**Klebsiella pneumonia 36 (31.8%)**	**Acinetobacter species 27 (24%)**	**Escherichia coli 15 (13%)**	**Serratia sp 10 (8.8%)**	**Pseudomonas aeruginosa 8 (7%)**	**Enterobacter species 5 (4.4%)**	**Burkhulderia cepacia 6 (5.3%)**	**Stenotrophomona Smaltophilia 3 (2.6%)**	**Salmonella Typhi 1 (0.88%)**	**Kingella Kingie 1 (0.88%)**
Ampicillin	100	100	100	100	Not tested	Not tested	Not tested	Not tested	100	Not tested
Co-amoxiclav	94	100	93	100	-			-	-	-
Ceftriaxone	94	88	73	80	-	100		-	0	100
Cefipime	83	55.5	60	40	25	80		-	-	-
Ceftazidime	94	88	73	80	75		33	33	-	-
Ciprofloxacin	69	70	86	80	50	60		-	100	100
Cotrimoxazole	61	78	46.6	50	-	40	16	0	100	0
Doxicycline	30	51	53	30	-	20		-	-	-
Amikacin	52	63	13	20	25	0		-	-	-
gentamycin	72	85	53	80	62	60		-	-	-
Imipenem	47	48	20	70	38	40		-	-	-
Meropenem	41.6	51.8	20	60	12.5	40	33	-	0	0
Piperacillin/ Tazobactum	66.6	77.7	46.6	60	62	80	-	-	-	-
Tigecycline	5.5	29	0	0	100	0	-	-	-	-
Polymyxin	8.3	3	0	Not tested	0	0	-	-	-	-

Table-IV: Antibiotic resistance pattern of Gram positive bacterial isolates.

Antibiotics	**Gram positive Isolates (n=56) (% Resistance to Antimicrobials)**		
	MRSA 25 (44.6%)	**MR-CONS 23 (41%)**	**Staphylococcus aureus 8 (14%)**
Amikacin	20	13	0
Co-amoxiclav	100	100	50
Ceftriaxone	100	100	37.5
Ciprofloxacin	60	52	75
Doxicycline	20	13	12
Gentamycin	60	48	37.5
Erythromycin	64	69.5	75
Clindamycin	60	48	37.5
Cotrimoxazole	36	34	50
Penicillin	100	100	87.5
Linezolid	0	34	0
Vancomycin	0	0	0

The study done by Tabah *et al*, reported an almost comparable rate of Carbapenem resistance to 38% in our study.[18] It was alarming to note that the isolates showed 8.3% resistance to Colistin and 5.5% resistance to Tigecycline, leaving limited therapeutic options and then posing a significant threat to the management of critically ill patients. Easy dissemination of this isolate and its ability to acquire multiple resistance mechanisms may worsen the scenario.

Acinetobacter baumannii was the second most common isolate causing sepsis in adult ICU patients, with most of the strains being XDR (63%), as reported by a study conducted in Georgia and India.[19]

Klebsiella pneumonia and *Acinetobacter Baumann's* resistance rate in our isolates was very high. 86.5% of Gram-negative organisms were MDR isolates. This result is in line with a study by Feleke *et al*, who reported 70% MDR isolates.[13] However, a lower percentage, 59% of MDR isolates, was reported by another study in Ethiopia.[20] The MDR isolates of our study were resistant mainly to Ampicillin, Co-Amoxiclav, Ciprofloxacin, Gentamicin, Cefotaxime/Ceftriaxone, and Imipenem. However, excellent results were noticed with both Polymixin and Tigecycline. Several studies also report similar observations.[21]

Escherichia coli was the third common pathogen in our study. These organisms were highly resistant to ampicillin (100%), 3rd generation Cephalosporins (>70%) and Ciprofloxacin (>80%). Similar results against the same isolate were reported by a study conducted in Bangladesh by Ahsan *et al*, reporting more than 60% resistance for 3rd generation Cephalosporins and ciprofloxacin.[22] However, none of the isolates was resistant to Colistin and Tigecycline. In our study, most isolated *Klebsiella pneumonia* (75%) were ESBL producing organisms. In contrast (25%) of isolated *Escherichia coli* were ESBL positive. Our results are in contrast to a study done by Sakellariou *et al*, reporting ESBL production mostly in *E.coli* (73.1%) than in

Klebsiella pneumonia (26.9%) isolated from the blood samples of septicaemic patients.[23]

Among 37.6% Carbapenems resistant organisms (CRO), 48.1% *Acinetobacter Baumannii* (CRAb) and 38.8% *Klebsiella Pneumonia* (CRKP) were documented, a study done in Greece and India also recognised the comparable frequency of Carbapenem resistance against the identical isolates taking them as a significant concern.[24]

Our study anticipated that sepsis due to gram-positive pathogens was associated with fewer complications and mortality than gram-negative isolates. As per our study, 33.1% of isolates were gram-positive. 44.6% were MRSA, 41% were MR-CONS, and 14.2% were *Staphylococcus aureus*. In contrast, a study in Ethiopia reported a higher 46.4% of gram-positive isolates.[11] Considering the significant number of *Methicillin-Resistant Staphylococcus Aureus* (MRSA), drugs like linezolid and Vancomycin/Teicoplanin are the available choice for the empirical treatment of MRSA. Antimicrobial resistance rate among all Gram-positive bacterial isolates was observed highest with Penicillins (98%), 3rd generation Cephalosporins (94.6%), Erythromycin (67%), followed by Ciprofloxacin (59%). A study done by Saeed *et al*, also observed the same susceptibility pattern for Gram-positive bacterial isolates.[14] Acquired resistance to Vancomycin was not found in this study which is in complete accordance with a study conducted by Wasihun *et al*.[25] Highly resistant bacterial infections, mainly MR-CONS is, associated mainly because of prolonged use of broad-spectrum antibiotics and prolonged usage of indwelling devices and endotracheal intubation.[14]

In our setup, carbapenems and glycopeptides such as Vancomycin/Teicoplanin are the chief agents to treat Gram-negative and Gram-positive sepsis. However, these should be used cautiously to prevent developing resistance against them.[23] A combination therapy will help keep in view the different isolates. The increasing trend of polymixin resistance has become an alarming concern. It should be clear that if there has been no practical, timely response, this challenge of antimicrobial resistance will become an alarming scenario and will become a significant challenge in the years to come.

Their susceptibility patterns indicate the sensitivity of commonly used antibiotics, i.e., third, generation Cephalosporins, Piperacillin/Tazobactam, Aminoglycosides and Imipenem towards these species. Other gram-negative isolates are going down, leaving behind limited treatment options. The above discussion would help start empirical therapy and effectively formulate an antibiotic policy to manage septicaemia. It is also essential to de-escalate according to the antimicrobial susceptibility report to shorten the period of morbidity and hence a better outcome.

CONCLUSION

The study of bacteriological profiles with antibiotic susceptibility/resistivity patterns plays a pivotal role in the effective management of bacteraemia cases. Early detection of causative pathogen and initiation of targeted therapy is the mainstay of treatment. Our study anticipated that gram-negative bacterias are predominant isolates responsible for adult sepsis. Among them, Klebsiella species and Acinetobacter species were the most common, respectively. The rising trends in antibiotic resistance emphasise the importance of hospital infection control policies and implementation of rational prescription of antimicrobial practices with continued surveillance to prevent the emergence and further spread of resistant bacterial pathogens.

Conflict of Intrest: None.

Author's Contribution

FTZ: Data collection and analysis, IAM: Data analysis and statistics, MZS: Data collection & analysis, WH:, FS:, Data collection, AA: Data collection and data analysis.

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