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Pattern of Antimicrobial Resistance and Outcomes of Patients with Sepsis admitted to a Tertiary Care Hospital in Peshawar: A Prospective study

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A B S T R A C T

Background: Sepsis is a life-threatening illness induced by a change in the host's reaction to various infections.

Objectives: To study the antimicrobial resistance patterns and outcomes in patients with sepsis admitted to a tertiary care hospital in Peshawar.

Methodology: In this prospective study sepsis patients were followed till an outcome was assigned to them. The data was collected and independent samples t-test, chi square test and multivariate logistic regression was used to study the effect of various dependent variables on mortality using SPSS version 25. A p-value of less than 0.05 was taken as significant.

Results: In 106 patients with sepsis the mean age was 44.5 years (SD=19.2 years) and 60.3% (n=64) were males. The overall mortality was 21.3% (n=23). Presence of DM (aOR: 6.1 CI:1.31-29.27.8, p-value=0.02), increasing age (aOR: 1.05, CI 1.007-1.104 p-value=0.025) and rising days of hospitalization (aOR:1.08, CI:1.003-1.16, p-value=0.041) had the strongest statistically significant relation with mortality. As compared to those admitted in the ICU, which was taken as reference, the chances of worst outcome were extremely low in those admitted to surgical unit (aOR: 0.027, CI:0.001-0.625, p-value=0.023). Hypertension (aOR:, CI:, p-value=0.74) and gender (aOR: 0.68, CI: 0.087-4.5, p-value= 0.62) had no positive correlation with mortality.

Conclusion: Our result demonstrates that the growth of rare organisms like B Cepacia and multi-resistant E. coli. The creation of a local antibiogram at the institutional, provincial, and national levels can aid in the prompt administration of culture sensitive antibiotics, allowing for better management of such cases.

Keywords: Sepsis; Antimicrobial Resistance; Outcomes; Antibiogram; Antibiotics

Introduction

Sepsis is a life-threatening condition that results from altered host response to infections caused by various pathogens.1 It usually results from the interplay of microbial pathogenicity and host immune responses.2 Despite the recent developments in the discoveries of antibiotics and newer diagnostic techniques, sepsis remains a leading cause of mortality and morbidity worldwide.3 One of the main reasons for the high mortality and morbidity is the rising antibiotic resistance.4 During the covid-19 pandemic, the threat of resistance became even more dangerous in this part of the world, where injudicious use of antibiotics was a common practice during the pandemic.[5]

Sepsis is among the leading cause of in-hospital mortality. According to 2017 data from WHO, sepsis harmed 49 million individuals and was responsible for nearly 11 million fatalities worldwide, or about 20 percent of all annual deaths in the world.[6] According to the findings, children and underprivileged populations from low and middle-income countries are particularly vulnerable to sepsis because of the delay in the administration of empirical antibiotics, the non-availability of local antibiogram, and not doing cultures in every case.[7] Data from Pakistan in general and Khyber Pakhtunkhwa in specific is deficient with only a few studies. One study done in the pediatric population reported mortality of 24%, with multiorgan dysfunction syndrome among 81% of the study population.[8] In another study done in the adult population, most patients reported abdominal sepsis with a mortality of 51.7% in the sepsis group compared to 17% in the non-sepsis group.[9]

Sepsis is usually diagnosed with a positive microbial culture from a body sample along with clinical manifestations of the disease.[10] The diagnosis is further supported by acute phase reactants and inflammatory markers like Interleukine-6 levels (IL-6), Procalcitonin, and highly sensitive C-reactive protein (HS-CRP).[11,12] The positive culture usually depends upon the time and type of the sample and the latest techniques to grow the culprit organism. In some of the cases, despite high suspicion of sepsis and positive inflammatory markers, culture results are negative.[13] Such cases pose a challenge and are usually treated empirically; moreover, Bacillus spp. Corynebacterium spp. and Propionibacterium acnes are more likely to cause contamination (5% risk of true bacteremia) when isolated from only one of two or more samples and when the sample becomes positive after 72 hours of incubation.[14] Different scoring systems are utilized for sepsis identification and prognosis, such as vital signs, systemic inflammatory response syndrome (SIRS), signs of infection, Quick Sequential Organ Failure Score (qSOFA) or Sequential Organ Failure Assessment (SOFA) criteria, National Early Warning Score (NEWS), or Modified Early Warning Score (MEWS) and APACHE score.[15]

Antimicrobials must be administered quickly in cases of sepsis if survival rates are to be improved.[16] According to several studies, the risk of death in patients with sepsis or septic shock increases with each additional hour of delay in the introduction of suitable antimicrobials.[17] Furthermore, individuals with sepsis and septic shock who fail to receive effective empirical treatment are more likely to die.[18] To ensure that all suspected pathogens, including bacteria, fungi, and viruses, are addressed, the Surviving Sepsis Campaign (SSC) recommendations advocate empiric broad-spectrum treatment with at least one antibiotic as soon as possible following the diagnosis of sepsis.[19]

Early suspicion, diagnosis, and institution of empirical antibiotics are critical to the successful management of sepsis. The current study emphasizes studying the resistance patterns of causative pathogens and outcomes of sepsis patients in a tertiary care hospital in Peshawar. To date, no such study has been performed in the hospital, and it is vital to know the antibiogram of the hospital in order to initiate effective and timely management to decrease the huge mortality associated with the disease.

Objectives

To study the antimicrobial resistance patterns and outcomes in patients with sepsis admitted to a tertiary care hospital in Peshawar.

Methodology

This study is based on the medical records of 108 culture-positive samples of patients with sepsis who were followed till an outcome was assigned to them, at a tertiary care hospital in Peshawar. The admitted patients were from various departments. The biological samples were collected in the form of respiratory tract secretions, pus, wound materials, urine, blood, and abdominal specimens like ascites or tissue samples. The collected samples were sent to the pathology laboratory, Lady reading hospital for culture and sensitivity. (Information about culture materials and methods) The reported culture of the patient and their outcome were then recorded from the (Hospital Management Information System) HMIS system.

The study was conducted from April 2020 to June 2020. Data about 106 individuals were collected and followed for an outcome i-e Death or discharge from the hospital. The outcome was successfully recorded for all of the 106 study participants with no dropouts. Information about age, gender, unit of admission, site of sampling, and presence of comorbidities were recorded in the preformed questionnaires from the HMIS.

Table 1. Demographic characteristics of the study population

Variables		Frequency	%
Age			
Mean (SD)yrs.		44.5(19.2)	
Gender			
Male Female		64 42	60.3 39.7
Unit of admission			
Surgical Medical ICU		38 60 8	35.8 56.6 7.5
Site of sample			
Blood Skin/Wound		10 38	9.5 35.9
Others	Urine Abdomen Respiratory tract	22 12 24	20.7 11.3 22.0
Days of Hospitalization			
Mean (SD)		12.3(9.5)	
Gram Stain			
Negative Positive Mixed		64 38 4	62.1 35.8 3.7
Organisms Grown			
Pseudomonas MSSA MRSA E Coli Others		20 14 25 37 10	18.9 13.2 23.6 34.9 9.4
Resistance to more than 2 drug classes			
Yes No		38 68	35.8 64.2
Resistance to 2 or less drug classes			
Yes No		42 64	39.6 60.3

Table 2. Presence of Comorbidities

Variables	Frequency	%
DM		
Yes No	50 52.8	47.2 52.8
HTN		
Yes No	12 94	11.3 88.7
CKD		
Yes No	8 98	7.5 92.4
Other		
Yes No	14 92	13.2 86.7

We calculated the cumulative survival, and the effect of various characteristics on mortality was studied with the help of the chi-square test, Fisher Exact test, and independent samples t-test. Adjusted odds ratios (aOR) for independent variables like age, days of hospitalization, site of sample, unit of admission, and presence of comorbidities were calculated using multivariate logistic regression. All the analysis was conducted in SPSS version 25. A priori was set at 0.05 to test statistical significance.

We used anonymized data for our study, which was reviewed and approved by the Institutional Review Board (IRB) of LRH.

Results

A total of 106 patients with positive culture samples were studied. The mean age of the study population was 44.5 years, with a standard deviation of 19.2. The minimum age was 11 years and the maximum was 91 years. 60.3% (n=64) were male. The average number of days of hospitalization were 12.5 days, with a standard deviation of 9.4 days, a minimum of 2 days, and a maximum of 50 days (Figure 1).

One-third (35.8%, n=38) of the patients were admitted in surgery and allied departments, like Gynae & Obs, Orthopedics, neurosurgery and general surgery units. 56.7% (n=60) were admitted in medical and allied wards like general medicine, cardiology, gastroenterology, endocrinology, and pulmonology. The remaining 7.5% (n=8) were admitted to the ICU. In 35.9% (n=38) of the cases, the sample was collected from surgical wounds, 9.5% (n=10) from blood, and 54.7% (n=58) from other sites, which includes respiratory tract samples 22.6% (n=), urine 20.7% (n=) and 11.3% from abdominal samples (Table 1).

As shown in table 2, diabetes was the most prevalent comorbidity, affecting 47.2% (n=50). Among the other comorbidities, 11.3% (n=12) had Hypertension, 7.5% (n=8) had chronic kidney disease, and 13.2% (n=14) had other comorbidities like COPD, Bronchiectasis, CLD, and Post TB fibrosis.

In 34.9% of the samples, growth of E Coli was detected (Table 1, Fig 2). 23.6% MRSA, 18.9% Pseudomonas, 13.2% MSSA, and 9.4% had other organisms. The ten organisms grouped into “Others” had some unusual growths like Burkholderia Cepacia and Coliform species. 60% (n=22/37) of the E Coli were grown in urine samples and about 27% were grown in abdominal samples. Majority of the respiratory samples had growth of staph aureus and Klebsiella. Moreover, 80% (n=16/20) of the pseudomonas aeruginosa were grown in wound samples as shown in Figure 2. Of all the samples, 35.8% were resistant to more than two drug classes. There were also some unusual resistance patterns found; in three cases, E Coli was resistant to Fosfomycin, and in two cases, it was resistant to Ertapenem. 70% of the E Coli grown were resistant to Ciprofloxacin.

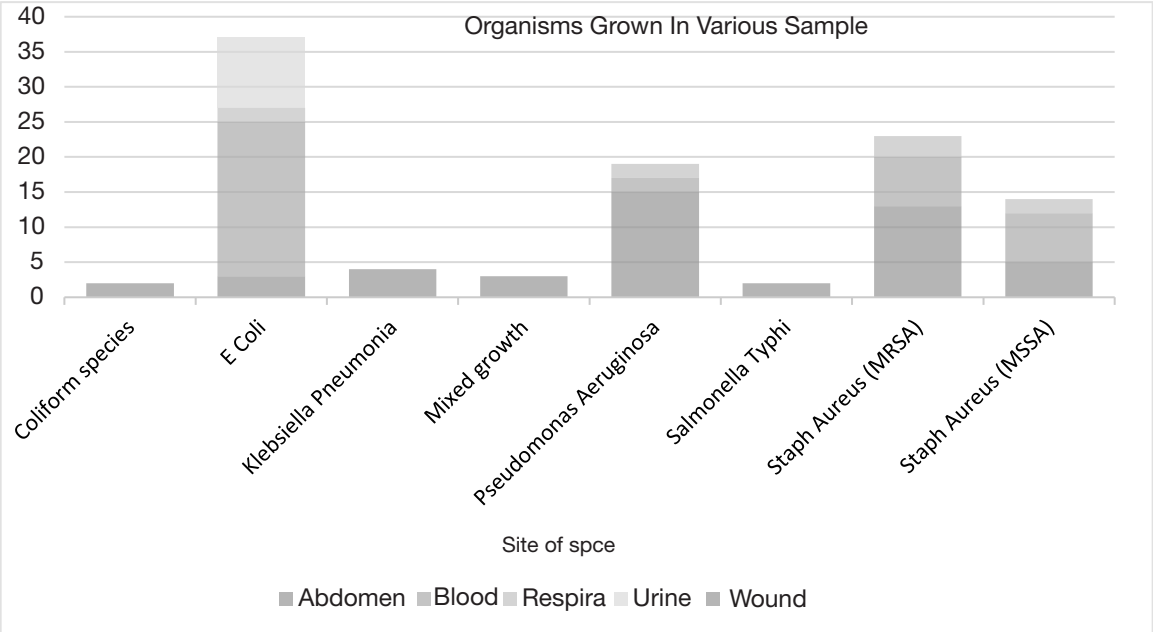

Figure 2. Organisms grown in various samples

There were 23 deaths in total with a mortality rate of 21.3%. It was highest in patients admitted in ICU (75%, n=6/8), and in those where culture was positive in the blood (50%, n=5/10). In patients who died, the mean age was 58.9 years compared to 40.4 years in the survivors. The relationship was statistically significant with a p-value of <0.001 (Table 2). On univariate analysis (table 2), increasing age (p-value= <0.001), male gender (p-value=0.048) rising days of hospitalization, mean days of 18.0 days in those who died compared to 10.9 days in the survivors (p-value=<0.001), admission to the ICU (p-value=0.001), culture positivity in blood samples (p-value=0.01), presence of comorbidities like DM (p-value=0.001), and CKD (p-value=0.011) were statistically

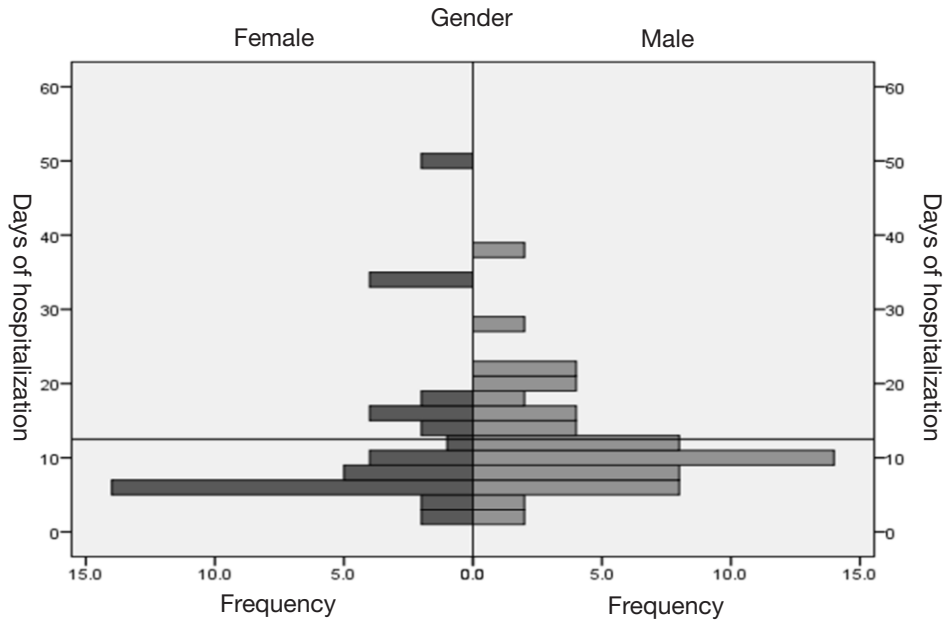

Figure 1. Gender and Hospitalization days-wise distribution of the study population. Blue=Females, Green= Males. The horizontal line shows mean days of hospitalization i-e 12.5 days.

Table 3. Correlation of various characteristics with mortality on Univariate Analysis

Variables	Outcome		Total	P-Value*
	Died	Survived		
Age				
Mean (SD) years	58.9(18.2)	40.4(17.2)	44.5(19.2)	<0.001***
Gender n (%)				
Male Female	18 (78.3) 5 (21.7)	46 (55.4) 37 (44.6)	64 (60.4) 42 (39.6)	0.048*
Unit of admission				
Surgical Medical ICU	4 (17.4) 13 (56.5) 6 (26.1)	34 (41.0) 47 (56.6) 2 (2.4)	38 (35.9) 60 (56.6) 8 (7.5)	<0.001**
Site of sample				
Blood Skin/Wound Other	5 (21.7) 4 (17.4) 14 (60.9)	5 (6.0) 34 (41.0) 44 (53.0)	10 (9.4) 38 (35.8) 58 (54.8)	0.019**
Days of Hospitalization				
Mean (SD)	18.0(9.5)	10.9(9.0)	12.5(9.4)	0.001***
DM				
Yes No	18 (78.3) 5 (21.7)	32 (38.5) 51 (61.5)	50 (47.1) 56 (52.9)	0.001*
HTN				
Yes No	6 (26.1) 17 (73.9)	6 (7.2) 77 (92.8)	12 (14.5) 94 (85.5)	0.021*
CKD				
Yes No	6 (26.1) 17 (73.9)	2 (2.4) 81 (97.6)	8 (7.5) 98 (92.5)	0.011**
Other				
Yes No	2 (8.7) 21 (91.3)	12 (14.5) 71(75.5)	14 (13.2) 92 (86.8)	0.53**

Gram Stain				
Negative Positive Mixed	11 (47.8) 12 (52.2) 0 (0)	53 (63.9) 26 (31.3) 4 (4.8)	64 (60.4) 38 (35.8) 4 (3.8)	0.13**
Organisms Grown				
Pseudomonas MSSA MRSA E Coli Others	3 (13.0) 3 (13.0) 7 (30.4) 8 (34.8) 2 (8.8)	17 (20.5) 11 (13.3) 18 (21.7) 29 (34.9) 8 (9.6)	20 (18.9) 14 (13.2) 25 (23.6) 37 (34.9) 10 (9.4)	0.88**
Resistance to more than 2 drug classes				
Yes No	7 (30.4) 16 (69.6)	31 (37.3) 52 (62.7)	38 (35.9) 68 (64.1)	0.54*
Resistance to 2 or less drug classes				
Yes No	16 (69.6) 7 (30.4)	48 (57.9) 35 (42.1)	64 (60.4) 42 (39.6)	0.30*

*p-value represents the result of the chi-square test

**p-value represent result of fisher exact test

*** p-value represents results of independent samples t-test

significant in terms of mortality. Resistance to more than two drug classes (p-value=0.54), and type of organisms grown (p-value= 0.88) had no statistically significant effect on mortality.

On multivariate logistic regression (table 3) presence of DM (aOR: 6.1 CI:1.31-29.27.8, p-value=0.02), increasing age (aOR: 1.05, CI 1.007-1.104 p-value=0.025) and rising days of hospitalization (aOR: 1.08, CI:1.003-1.16 p-value=0.041) had the strongest statistically significant relation with mortality. As compared to those admitted in the ICU, which was taken as reference, the chances of worst outcome were extremely low in those admitted to the surgical (aOR: 0.027, CI: 0.001-0.625, p-value=0.023) and medical unit (aOR: 0.101, CI: 0.01-1.07, p-value=0.05).

Discussion

The observations of the current study revealed a high mortality (21%) and rising burden of organisms resistant to first-line antimicrobials. The main pathogen observed in the samples was E Coli (34.9%). It mainly grew in urinary and abdominal samples. Among the other organisms were Pseudomonas, MRSA, MSSA, and Others, including Klebsiella, coliform species, and salmonella typhi. The same finding was reported by many other studies done in round the globe. In one study conducted by Muzammil M et al, E Coli grew by 39.6 %, followed by enterococcus, pseudomonas and MRSA(20). In the majority of the cases, the E Coli in our study was resistant to fluoroquinolones. And in some cases, it was resistant to Fosfomycin and ertapenem, which is alarming for future antimicrobial stewardship. Furthermore, the most common drug used against E Coli, in our study, was Fosfomycin.

The second most common pathogen in our study was MRSA. It grew in 23% of the samples and carried the highest mortality figures, with nine deaths among the 25 samples. In most cases, the patients did not receive drugs covering MRSA and were later switched on after the culture reports, which might have been responsible for the high mortality. Other similar studies have also reported with high mortality from MRSA. In one study, the 90 days all-cause mortality in patients with positive culture for MRSA was 31.5%.[21] MRSA, in our study, was mainly isolated from respiratory samples. More than half of the staph aureus growths in our study turned out to be resistant to methicillin. This observation guides us to be

Table 4. Multivariate Logistic regression

Characteristics	aOR	95% C.I.s		p-value
		Lower	Upper	
*Age	1.05	1.007	1.104	0.025
Gender				
Female	Ref			
Male	0.75	0.155	3.704	0.73
***Unit of admission**				
ICU	Ref			
Medical Units	0.101	0.01	1.07	0.058
Surgical Units	0.027	0.001	0.625	0.023
***Sampling Site**				
Surgical Wounds	Ref			
Blood	3.67	0.215	62.57	0.12
Others	2.26	0.313	16.44	
Hypertension				
No	Ref			
Yes	0.90	0.097	8.499	0.93
***Diabetes Mellitus**				
No	Ref			
Yes	6.1	1.31	29.27	0.021
*Days of Hospitalization	1.08	1.003	1.16	0.041

more cautious in managing patients with respiratory symptoms, who should be empirically started on antibiotics covering MRSA. The third most common pathogen in our observation was pseudomonas. As expected, it mostly grew in surgical cases like samples from wound cultures. In a few cases, pseudomonas was isolated from respiratory samples as well. Similar studies also show the same pattern and percentages of organism growths.[22]

The overall mortality in our study is 21.3%. Older age, increasing days of hospitalization, and the presence of comorbidities were strongly correlated with mortality. We should be cautious in dealing with older age patients, patients with comorbidities and those who stays for long in the hospital. The other factors which had a positive correlation with mortality are organisms growing in blood samples and those admitted to the ICU. Age has been declared an independent risk factor for mortality in culture-positive elderly patients by Martin GS et al,[23] who found that elderly patients had relative risk of 13.1 as

compared to younger age groups. Different studies have also positively linked the presence of diabetes, admission to ICU, and increasing length of stay in hospital to mortality.[24] Contrary to our study, Molina F et al, in their survey have found no significant relation between hospital length of stay and mortality.[25]

Here we also observed the growth of some unusual organisms like Burkholderia cepacia, multi-resistant E Coli and Non-tubercular mycobacteria. In three cases, in our study, the E-Coli isolates were resistant to ertapenem. Ertapenem resistance, in other studies, has been explained by a defect in outer membrane protein and the production of extended-spectrum B-Lactamase.[26] The Burkholderia cepacia isolated in our study was only sensitive to colistin, polymyxin, and fusidic acid. We need to report such cases and develop a proper antibiogram for such cases to be dealt with timely administration of antibiotics. B Cepacia is an unusual cause of sepsis and its transmission is mainly due to human contact with heavily contaminated medical devices and disinfectants.[27] Hospital authorities must routinely check these supplies for any such contamination and report it timely. Another reason for increasing B Cepacia might be the increasing use of the organism in the agriculture industry as a pesticide.[28] This needs further research on whether the species used by agriculturists can affect humans or not.

Conclusion

According to our findings, there were growth of pathogens resistant to various drug classes, responsible for high mortality and morbidity. Apart from the common pathogens, we have witnessed growth of rare organisms like B Cepacia and multiresistant E. coli. Moreover, higher age, rising days of hospitalization and presence of comorbidities like DM and ESRD were responsible for high mortality in patients with sepsis. With the development of local antibiogram at the institutional, provincial, and national levels it can help us to guide the timely commencement of drug sensitive antibiotics, and thus will be decreasing the huge mortality and morbidity associated with sepsis.

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