ORIGINAL ARTICLE
OUTCOMES OF INTENSIVE CARE PATIENTS HAVING SEPTIC SHOCK AT A TERTIARY CARE HOSPITAL OF ISLAMABAD

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Background: Septic shock is defined as sepsis with circulatory, cellular and metabolic abnormalities which are associated with greater mortality more than 40%. The objective of this study was to identify shortcomings and act promptly and adequately. **Methods:** This case series included 32 patients over a period of 03 months, September to November 2016 done at ICU of KRL Hospital Islamabad. **Results:** The study only enrolled patients who fulfilled the criteria of septic shock. Mortality was as high as 50%. (UTI) was the most common infection (43.75%). In patients who died Pneumonia was commonest infection (43.75%). Mean TLC, CRP and lactate was 17.48×10^9/l, 29.28 mg/L and 6.81mmom/L respectively. Escherichia Coli (*E. coli*) was the most common isolated pathogen (31.25%) followed by Staphylococcus Aureus (12.5%). Mean initial MAP was 49.7 mmHg and mean MAP at end of 3-day period was 71.4 mmHg. Mean norepinephrine dose given on day 1, 2 & 3 was 0.90 µg/kg/min, 1.01 µg/kg/min & 1.28 µg/kg/min respectively. Mean hospital stay was 7.1 days. Six out of 08 (75%) patients who needed ventilator support died while 02 out of 08 (25%) patients survived. Acute Kidney Injury (AKI) was the most common End Organ Damage (EOD). **Conclusion:** Mortality remains high in septic shock despite maximum efforts. In current study MAP, serum lactate level, hospital stay, need for ventilator support, comorbidities, need for newer generation antimicrobials were the important cofounders in differentiating patients who died and those who survived with significant p-values in the 1st four conditions.
Keywords: Sepsis; Septic Shock; Infection; TLC; CRP; serum Lactate; Norepinephrine; Multi Organ Failure (MOF); MAP; Antimicrobials

INTRODUCTION

Sepsis is a clinical syndrome that has biologic, physiologic and biochemical abnormalities and is described as systemic inflammation secondary to infection. Sepsis and the resultant inflammatory response can cause multiple organ dysfunction syndrome and even death. Large number of cases of sepsis occur worldwide.[1] With most appropriate treatment it is appraised that over 10 % patient die of sepsis and mortality is estimated to be over 40 % for patients presenting with septic shock.[2] Infection can occur if a normally sterile tissue is invaded by some organism that can cause infectious pathology and bacteraemia is defined as the presence of viable bacteria in blood. Analysis of an international database conveyed that 437 per 100000 person-years suffered from sepsis between the years 1995 and 2015 though this data was taken from high income countries only.[3] Due to increased prevalence of respiratory infections in winter, incidence of sepsis is greater during winter season.[4] Sixty to 85 % of the patients presenting with sepsis are older patients equal or more than 65 years of age.[5] Approximately half of the cases of sepsis have no identifiable source, i.e., are culture negative.[6] In a study conducted in USA, gram positive bacteria were most frequently identified in patients with sepsis while a considerable number of patients had gram negative sepsis. Along with that it was also found that incidence of fungal sepsis has also increased.[7] According to Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM), Sepsis is defined as a life-threatening organ dysfunction caused by dysregulated host response to an infection. Organ dysfunction is defined as an increase in Sequential Organ Failure Assessment (SOFA) score equal or more than 2. The SOFA score was initially designed to sequentially assess the severity of organ dysfunction in patients who were critically ill from sepsis. The original SOFA instrument was derived from a cohort of 1449 patients admitted to 40 ICUs in 16 countries.[8] Symptoms, signs, radiologic data, microbiologic data and response to therapy are the parameters that can help identify an infection. PaO_2/FiO_2 (P/F) ratio, amount of vasoactive medication needed to prevent hypotension, bilirubin level, platelet concentration, Glasgow Coma Scale (GCS), serum creatinine or urine output are the measurements of organ dysfunction defining SOFA score.[9] In Septic shock patients despite optimum fluid resuscitation, require vasoactive medications to maintain mean arterial pressure (MAP) equal or more than 65 mmHg and have lactate level more than 2 mmol/L (more than 18 mg/dL). Septic shock is also defined as sepsis with circulatory, cellular and metabolic abnormalities which are associated with greater mortality.[8] Multiple organ dysfunction syndrome (MODS) refers to progressive

dysfunction of different organs in acutely ill patient. MODS can be primary and secondary. There are certain risk factors which put patients at a high level of adverse outcome. These include, advance age, immunosuppression, diabetes, cancer, previous hospitalization, community acquired pneumonia (CAP), intensive care unit (ICU) admission, genetic factors and bacteraemia. Approximately 50% of ICU patients have nosocomial infection and are more prone to develop sepsis and septic shock.[10] According to one study conducted on patients with CAP, 48% developed sepsis and 5% developed septic shock.[11] Previous hospitalization was associated with three fold increased risk of developing sepsis within next 90 days.[12] In a study conducted on patients with bacteraemia, 95% of positive blood cultures were associated with development of sepsis or septic shock.[13] Intravenous antibiotics should be administered as soon as possible and in case the source is unknown and pseudomonas is unlikely combination of vancomycin with third or fourth generation cephalosporin or beta lactamase inhibitor or carbapenems are the choices and in case pseudomonas is likely vancomycin should be combined with anti-pseudomonal agent.[14] Vasopressors are the second line agents in the management of septic shock and intravenous fluids are recommended as long as they don't impair gas exchange.[15] Norepinephrine is the preferred choice of drug and incase arrhythmias preclude its use, phenylephrine is used.[16] Inotropic agent (dobutamine) is used in case of refractory cases and in patients who have low cardiac output.[17] We in Pakistan lack local data regarding frequency of infections, comorbid conditions, valuable laboratory investigations, common pathogens, antimicrobial sensitivity, vasopressor dosage, MAP, hospital stay, ventilator support, end organ damage (EOD) etc. This data is necessary to guide our ICUs in developing an approach which may improve patient care.

MATERIAL AND METHOD

This case series included 32 patients from Islamabad and Rawalpindi region during a period of 3 months, September to November 2016 done at ICU of KRL Hospital Islamabad. Patients who fulfilled the criteria of septic shock were included in the study.

Patients were managed according to surviving sepsis campaign (SCC) guidelines. After initial fluid therapy and antimicrobial administration patients were given vasopressors as per the judgement of physician in-order to maintain the MAP more than 65 mmHg and Nor-Epinephrine was the 1st choice of vasopressor given.

Patients included in the study were equal or more than 18 years of age and fulfilled the definition of septic shock according to Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) criteria.

The collected data included age, gender, current diagnosis, comorbid condition, total leucocyte count (TLC), C-reactive protein (CRP), serum lactate, ventilator status, cultured pathogens, culture based antimicrobial agents, 3-day dose of norepinephrine used, stay in hospital, EOD, MAP and outcome in terms of death or survival. The study was approved by Ethical review board of KRL Hospital Islamabad, Pakistan.

Separate analysis was done on SPSS-20. Statistical significance was indicated if p-value was ≤0.05. The clinical data of the study patients were stated as Mean. The difference between two groups were examined by t-test or ANOVA for continuous variables and by c2-test for categorical variables. Chi-square test was also applied to check for association between two categorical variables.

RESULTS

There was a total of 32 patients included in our study out of which 14 were males and 18 were females. Mortality rate was 50%, i.e., 16 patients included in the study died. Out of the 16 patients who died, 08 were males and 08 were females.

Mean age in complete study group was 66.41 years, in survivors mean age was 65.69 years and in non-survivors it was 67.13 years. There was no significant difference in terms of age among survivors and non-survivors. p-value >0.05.

Table-1 shows clinical conditions leading to septic shock. Urinary Tract Infection [UTI] 08 (25%) was the most common followed by Pneumonia 06 (18.75%). Table-2 shows a comparison of disease conditions in patients who survived with those who died. In case of survivor's common comorbid conditions included Diabetes Mellitus [DM] (18.8%) followed by Hypertension (HTN) & cerebrovascular accident [CVA] (12.5%). In Non-survivor group HTN & DM were common (12.5%). Table 3 demonstrates detail of comorbid conditions in survivor & non-survivor group.

In complete study group TLC was raised in majority of the patients. Mean TLC was 17.48×10^9/l. CRP was raised in all patients. Mean CRP was 29.28 mg/L. Serum Lactate was also raised in all patients. Mean Serum Lactate was 6.81 mmol/L. Serum lactate levels were statistically significant among survivors and non-survivors, p-value <0.05. These findings are depicted in table-4.

Table-5 shows a comparison of bacterial isolates among survivors and non-survivors. Escherichia coli (*E. coli*) was the commonest isolate in both groups. Table-6 illustrates the percentages of sensitive antimicrobials.

In complete study group, initial MAP was less than 65 mmHg in all patients. Mean MAP was 49.68 mmHg. In survivors mean MAP was 49.12 mmHg

while in non-survivors mean MAP was 50.25 mmHg. At the end of 3-day period, overall MAP had variations. Mean MAP was 71.37 mmHg. In survivors mean MAP was 79.62 mmHg while in non-survivors mean MAP was 63.12 mmHg. At the end of 3-day period there was significant correlation among survivors and non-survivors in terms of MAP, *p*-value <0.05. Findings are explained in table-7. Norepinephrine was the vasopressor administered. In complete study group on day 1 mean dose administered was 0.90 µg/kg/min. On day 2 mean dose administered was 1.01 µg/kg/min.

On day 3 mean dose administered was 1.28 µg/kg/min.

In complete study group mean stay in hospital was 7.06 days. There was a significant association among survivors and nor-survivors, *p*-value <0.05. Table 8a illustrates the details. A total of 08 patients were given ventilator support. Two (25%) patients survived and 06 (75%) died. Table 8b demonstrates the details. Significant association was noted in terms of ventilator support among survivors and non-survivors, *p*-value <0.05. In complete study group EOD was noted in 23 (71.87%) cases. Table 8c explains the details.

Table-1: Diagnosis along with number of patients and percentages

Diagnosis	Number of Patients	Percentage (%)
Urinary Tract Infection (UTI)	08	25
Pneumonia	06	18.7
Acute Gastroenteritis (AGE)	03	9.4
Pneumonia, UTI	03	9.4
Viral Encephalitis	02	6.3
Infected Bed Sores	01	3.1
Infective Endocarditis	01	3.1
UTI, AGE	01	3.1
UTI, AGE, Obstructive Uropathy	01	3.1
AGE, Non B,C Cirrhosis, Upper GI-Bleed	01	3.1
Osteomyelitis	01	3.1
Pyogenic Meningitis	01	3.1
Pneumonia, Infected Bed Sores	01	3.1
Pyohydronephrosis	01	3.1
UTI, Infected Bed Sores	01	3.1

Table-2: Diagnosis, number of patients and percentages in survivor and non-survivor group

Survivor Group			Non-Survivor Group		
Diagnosis	Patients	%	Diagnosis	Patients	%
Urinary Tract Infection (UTI)	06	37.5	Pneumonia	04	25
Pneumonia	02	12.5	Pneumonia, UTI	03	18.8
Acute Gastroenteritis (AGE)	02	12.5	Urinary Tract Infection	02	12.5
Viral Encephalitis	01	6.3	Viral Encephalitis	01	6.3
UTI, AGE, Obstructive Uropathy	01	6.3	Infected Bed Sores	01	6.3
Pyohydronephrosis	01	6.3	Infective Endocarditis	01	6.3
UTI, AGE	01	6.3	Pyogenic Meningitis	01	6.3
Osteomyelitis	01	6.3	AGE	01	6.3
Infective Endocarditis	01	6.3	AGE, Non B, C Cirrhosis, Upper GI-Bleed	01	6.3
			UTI, Infected Bed Sores	01	6.3

Table-3: Counts and percentages of comorbid conditions in survivor and non-survivor group

Comorbid Conditions					
Survivor Group			Non-Survivor Group		
Comorbid Condition	Patients	%	Comorbid Condition	Patients	%
Diabetes Mellitus (DM)	03	18.8	Hypertension (HTN) & Diabetes Mellitus (DM)	02	12.5
Hypertension & CVA	02	12.5	None	02	12.5
None	02	12.5	CKD & TB	01	6.2
Benign Prostatic Hyperplasia	01	6.2	HTN & COPD	01	6.2
COPD	01	6.2	CVA & DVT	01	6.2
DM & CKD	01	6.2	Non-Hodgkin Lymphoma & IHD	01	6.2
DM, HTN, IHD & CVA	01	6.2	Oesophageal Carcinoma	01	6.2
HTN, CLD, Hypothyroidism	01	6.2	HTN, IHD & CVA	01	6.2
DM & HTN	01	6.2	DCLD	01	6.2
HTN, IHD & CVA	01	6.2	DM, HTN, IHD & CKD	01	6.2
HTN & CVA	01	6.2	DM, HTN & COPD	01	6.2
HTN & Pott's Disease	01	6.2	DM, HTN & IHD	01	6.2
			IHD & CVA	01	6.2
			DM & SOL Brain	01	6.2

Table-4: TLC, CRP & serum Lactate levels in survivors & non-survivors.

	TLC (10^9/l)		CRP (mg/L)		Lactate (mmol/L)	
	Survivors	Non-Survivors	Survivors	Non-Survivors	Survivors	Non-Survivors
Mean	17.39	17.58	29.75	28.81	6.75	6.88
SD	6.88	5.52	15.26	11.19	1.29	2.36
Minimum	10	8.40	10	15	05	03
Maximum	34	30.40	58	60	09	11
p-Value	>0.05 (0.50)		>0.05 (0.19)		<0.05 (0.01)	

Table-5: Cultured Pathogens along with percentages in survivor & non-survivor group.

Cultured Pathogens			
Survivors		**Non- Survivors**	
Organisms	**Percentage**	**Organisms**	**Percentage**
None	50	None	56.2
Escherichia Coli	37.5	*Escherichia Coli*	12.5
E. coli, Acinetobacter	6.2	*E. coli*, Staph. Aureus	6.2
Staphylococcus Aureus	6.2	*Enterococcus faecum*	6.2
		Staphylococcus aureus	6.2
		Staph. Aureus, Proteus Vulgaris	6.2
		Strep. Pneumonia, Acinetobacter	6.2

Table-6: Antimicrobial sensitivity in survivors & non-survivors.

Antimicrobials sensitivity					
Complete Study Group		**Survivors**		**Non-Survivors**	
Antimicrobials	**%**	**Antimicrobials**	**%**	**Antimicrobials**	**%**
Ceftriaxone	28.1	Ceftriaxone	50	Pipercillin + Tazobactam	18.8
Meropenem & Moxifloxacin	15.6	Ceftriaxone & Moxifloxacin	12.5	Meropenem & Moxifloxacin	18.8
Cefoperazone + Sulbactam	9.4	Meropenem & Moxifloxacin	12.5	Cefoperazone + Sulbactam	12.5
Pipercillin + Tazobactam	9.4	Meropenem, Linezolid & Vancomycin	6.2	Meropenem & Amikacin	6.2
Ceftriaxone & Moxifloxacin	6.2	Cefoperazone + Sulbactam	6.2	Meropenem, Moxifloxacin & Imipenem	6.2
Meropenem & Amikacin	3.1	Cefoperazone + Sulbactam, Colomycin and Vancomycin	6.2	Meropenem, Moxifloxacin & Tigicycline	6.2
Meropenem, Moxifloxacin & Imipenem	3.1	Imipenem	6.2	Meropenem & Vancomycin	6.2
Meropenem, Moxifloxacin & Tigicycline	3.1			Ceftriaxone	6.2
Meropenem & Vancomycin	3.1			Cefoperazone + Sulbactam & Moxifloxacin	6.2
Meropenem, Vancomycin Linezolid	3.1			Cefoperazone + Sulbactam, Moxifloxacin & Vancomycin	6.2
Cefoperazone + Sulbactam & Moxifloxacin	3.1			Pipercillin + Tazobactam & Moxifloxacin	6.2
Cefoperazone + Sulbactam, Meropenem & Moxifloxacin	3.1				
Cefoperazone + Sulbactam, Vancomycin & Colomycin	3.1				
Pipercillin + Tazobactam & Moxifloxacin	3.1				
Imipenem	3.1				

Table-7: Initial and End of 3 days Mean Arterial Pressure (MAP) in complete study group, survivors and non-survivors.

	Complete Study Group MAP (mmHg)		**Initial MAP (mmHg)**		**MAP after 3 Days (mmHg)**	
	Initial MAP	MAP after 3 Days	Survivors	Non-Survivors	Survivors	Non-Survivors
Mean	49.68	71.37	49.12	50.25	79.62	63.12
Mode	50	77	46	50	77	73
Minimum	38	48	39	38	74	48
Maximum	64	88	59	64	88	73
p Value	>0.05 (0.97)		>0.05 (0.71)		< 0.05 (0.03)	

Table-8 (a, b & c): a; Hospital Stay in days among complete study group, survivors & non-survivors, b; ventilator support in survivors & non-survivors, c; End Organ Damage in percentages among complete study group, survivors & non-survivors.

a)	**Hospital Stay (Days)**		
	Total	**Survivors**	**Non-Survivors**
Mean	7.06	8.94	5.25
Minimum	02	04	02
Maximum	18	18	12
p-Value		<0.05 (0.01)	

b)	**Ventilator Support (08 Patients)**
Survivors	**Non-Survivors**
25% (02 Patients)	75% (06 Patients)
p-Value <0.05 (0.001)	

c) End Organ Damage (EOD)					
Complete Study Group		**Survivors**		**Non-Survivors**	
EOD	**%**	**EOD**	**%**	**EOD**	**%**
None	28.1	None	50	MOF	43.8
Acute Kidney Injury (AKI)	25	AKI	43.8	Respiratory Failure	25
MOF	21.9	Arrhythmia	6.2	Brain Stem Death	18.8
Respiratory Failure	12.5			AKI	6.2
Brain Stem Death	9.4			None	6.2
Arrhythmia	3.1				

DISCUSSION

Present study is unique in the sense that it only enrolled patients who had Septic Shock. As we know that mortality of septic shock is as high as more than 40% as reported in international literature.[2] In a study conducted in Karachi severe sepsis was present in 52% cases, and overall mortality was 35.1%.[22] In present study mortality was 50% although included patients had septic shock along with other serious comorbid conditions. Male and female distribution in terms of mortality was equal, though in a study conducted in Karachi males with sepsis had a 70% greater mortality rate as compared to females. This higher mortality appears to be related to differences in respiratory tract infection rate and IL-6 plasma levels, between the genders.[24]

Patients who died, Pneumonia was common (43.7%) and in survivors UTI was the most common infection (50%). Our results were similar to the results of a study conducted at Lahore in which UTI (46%) was the most common infection followed by Pneumonia (32%), Gastroenteritis (16%) and others (06%).[20] In one study mortality from sepsis was 50–55 percent when the source of infection was unknown, gastrointestinal, or pulmonary, compared with only 30 percent when the source of infection was the urinary tract.[23] In our study bacterial cultures were negative in 50% of surviving patients and 56.2% of patients who died of septic shock. In terms of comorbid conditions HTN (46.9%) was the most common followed by DM (37.5%). In a study conducted at Karachi HTN (45.5%) was the most common comorbid condition among patients with sepsis and septic shock followed by DM (40%).[24]

In present study leucocytosis was seen in all except one patient. No significance was found among both groups in terms of TLC p-value >0.05. CRP is an acute phase reactant which is raised in inflammation and tissue injury. It acts as pro-inflammatory as well as anti-inflammatory though its anti-inflammatory action predominates.[19] In our study CRP was raised in all patients but no significance was found among both groups in terms of CRP, p-value >0.05. In a paper, it was concluded that CRP concentration, with its rapid and cheap measurement, may be a good partner to refine the diagnosis of infection.[25] Elevated serum lactate can be an indicator of organ hypo-perfusion and is defined as lactate more than 2 mmol/L. Elevated serum lactate is associated with poor prognosis.[21] In our study serum lactate levels were raised in all patients and statistical significance was noted among survivors and non-survivors, p-

value <0.05. In a study, it was found that serial lactate monitoring in the emergency department (ED) patients with severe sepsis and septic shock is associated with an increase in crystalloid administration, resuscitation interventions, and improved clinical outcomes.[26] These findings emphasize on the need of lactate measurement in terms of adequate management.

In present study, it was found that *E. coli* was the most common isolated pathogen followed by Staphylococcus Aureus. A study conducted in Lahore also reveal *E. coli* (44.5%) as the most common pathogen responsible for sepsis in ICU settings.[20] In another study conducted in Karachi Salmonella typhi was the most common pathogen accounting for 18% positive cultures.[22] Overall 53.1% of cases showed no growth on cultures. This can be due to multiple reasons including inappropriate technique, transportation or antimicrobial use before admission. Among survivors Ceftriaxone was the most sensitive antimicrobial and among non-survivors Pipercillin+Tazobactam, Meropenem and Moxifloxacin combined were most sensitive. This indicates that among patients who died pathogens were sensitive to newer antimicrobials.

MAP is defined as [(2× diastolic) + systolic]/3. MAP less than 65 signifies hypo-perfusion and need urgent intervention. In present study, initial MAP was below 65 in all patients and with management it had risen. At the end of 3-day period there was significant correlation among survivors and non-survivors in terms of MAP, p-value <0.05 which shows that a rise in MAP may improve outcome. In a multicentre study, it was demonstrated that the time spent with MAP <55 mmHg was associated with increased risk of death.[29] Norepinephrine was the vasopressor started as soon as patients with MAP less than 65 mmHg did not respond to fluid resuscitation.

Mortality was low for patients who stayed for longer period of time in Hospital as compared to those who stayed for shorter period of time, p-value <0.05. Maximum patients who needed ventilator support died and significant association was noted among survivors and non-survivors, p-value <0.05 which shows that need for mechanical ventilation is a poor prognostic factor among patients with septic shock. In our study, Acute Kidney Injury (AKI) was the most common EOD followed by Multi Organ Failure (MOF). Among survivors AKI was common and among non-survivors MOF was common. These findings indicate that MOF is a poor prognostic factor among patients with septic shock. Schrier RW, *et. al*. had reported Sepsis as a cause of renal

insufficiency in 30–60% of patients, up to half of whom require dialysis.[27] In a study it was postulated that MOF occurred more frequently in patients with sepsis, irrespective of the time of onset.[28]

CONCLUSION

Mortality remains high in septic shock despite modern ICUs, trained staff, ease of availability of support services including ventilators, newer generation antimicrobials and vasopressor agents. Emphasis lies on proper attending of patients by general physicians and referral services before sending to tertiary care units. Unnecessary delay should at best be avoided. In current study MAP, serum lactate level, hospital stay and need for ventilator support were the important cofounders in differentiating patients who died and those who survived with significant p-values.

ACKNOWLEDGEMENT

AUTHORS' CONTRIBUTION

AA: Concept, design, analysis and interpretation of data. ASA: Literature review and data analysis. MS: Literature review and data collection.

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