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Outcome of Septic Shock and Associated Factors at the University of Gondar Hospital: A Retrospective Cohort Study

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Abstract

Background: Septic shock is a medical emergency causing significant morbidity and mortality. Multiple factors affect the outcome of septic shock in a particular clinical setting. Identifying factors associated with poor treatment outcomes is crucial for the improvement of medical care in patients with septic shock.

Objectives: The aim of this study was to determine the outcome of septic shock treatment and to determine factors associated with poor outcome.

Methods: A hospital based medical record review of patients admitted to the University of Gondar Hospital with the diagnosis of septic shock from January 2014 to October 2016 was conducted. Socio-demographic, clinical history and laboratory data were collected. Data entry and analysis was done using SPSS version 20.

Results: Ninety eight cases of septic shock fulfilled the criteria for analysis. The most common source of infection was the gastrointestinal tract. The in Hospital mortality rate of septic shock is 42 %. Longer duration of illness, presence of co morbidity and corticosteroid use negatively affected the outcome of septic shock. The types of vasopressor used had no effect on the outcome of septic shock.

Conclusion and recommendations: Septic shock has high mortality in Gondar, Ethiopia, where nearly half of the patients had died. Strategies shall be paved to let patients with possible septic shock visit health facilities early and patients with co-morbidities need a more vigilant care. Management strategies with prompt goal directed therapy is essential for a better outcome. It is highly recommended to have a hospital protocol for septic shock management. There is an urgent need for in depth analysis of the management approach and identifying the gaps and improving the patient care.

Keywords: Septic shock, Outcome, Gondar, Ethiopia

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Abbreviations: AOR- Adjusted Odds- Ratio; CKD-Chronic Kidney Disease; CLD-Chronic Liver Disease; COPD-Chronic Obstructive Liver Disease; COR-Crudes Odds Ratio; DM-Diabetes Mellitus; HIV-Human Immune Deficiency Virus; SPSS-Statistical Package for the Social Sciences; SIRS- Systemic Inflammatory Respiratory Syndrome; SOFA- Sepsis Related-Organ Failure Assessment; mg-Miligram; dL- Deciliter; EGDT- Early Goal Directed Therapy; MICU-Medical Intensive Care Unit; MDR TB-Multidrug Resistant Tuberculosis; mmHg-Millimeter Mercury; USA-United States of America; VL- Visceral Leishmaniasis; µL-Microliter.

Introduction

According to the old sepsis definition, basics to the understanding of septic shock are defining systemic inflammatory response syndrome (SIRS) and sepsis. SIRS is diagnosed when a patient shows more than one of the following four clinical characteristics: {1} body temperature > 38°C or < 36°C; {2} heart rate > 90 beats/

min; {3} hyperventilation, evidenced by a respiratory rate > 20 breaths/min or PaCO2 < 32 mmHg; and {4} white blood cell count > 12 000 cells/μL or < 4 000 cells/μL or with > 10% immature forms [1-3]. Sepsis is clinically appreciable when there is SIRS with suspected or evidenced microbial invasion. Severe sepsis is sepsis leading to variable degrees of organ dysfunction. Septic shock is severe sepsis with cardiovascular dysfunction manifesting with persistent arterial hypotension regardless of adequate fluid resuscitation [1,2,4]. Inline to the most recent sepsis 3 definition, Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction is represented by an increase in the Sepsis related-Organ Failure Assessment (SOFA) score of 2 points or more (Alteration in mental status, Decrease in systolic blood pressure of less than 100 mmHg, and Respiration rate greater than 22 breaths/min). Septic shock is defined as a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a higher risk of mortality. Patients with septic shock can clinically be identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia [5].

The incidence of septic shock is increasing on global scale. Despite advances in recognition and treatment of septic shock, hospital mortality remains alarmingly high, with rates ranging from 30% to over 50% in recent publications [6-10].

Early and aggressive fluid resuscitation has been suggested to have a critical role in optimization of organ perfusion, preservation of end organ function and improvement of survival [7,11-13].

Septicemia is the tenth leading cause of death in the United States of America (USA) based on 2004 data from the National Center for Health Statistics. Even though, the epidemiology of severe sepsis and septic shock remains poorly understood in developing countries, it is believed to be disproportionately high due to environmental degradation, widespread malnutrition, and higher rates of bacterial, parasitic, and human immunodeficiency virus (HIV) infections [14-16].

It is believed that evidence based interventions decrease sepsis related mortality. Selected evidence based practice recommendations have been developed to improve the outcome of severe sepsis and septic shock. The care bundles include the six hour resuscitation bundle and the 24 hour management bundle. Early Goal Directed Therapy (EGDT), which includes early initiation of hemodynamic resuscitation with specified treatment endpoints, has improved mortality rates in numerous clinical trials [17-19].

Delayed initiation of antimicrobial therapy increases mortality associated with septic shock. Several co morbid conditions are also associated with poorer outcomes for patients with septic shock. Except for refractory cases of septic shock, use of corticosteroid at baseline has shown no benefit. The presence of sepsis related organ dysfunction is associated with poor outcomes in septic shock [7,11,12,17-22].

Vasopressors are the cornerstone of the management of septic shock following adequate fluid resuscitation. The 2012 Surviving Sepsis Campaign Guideline recommends that vasopressor support be started for fluid refractory shock as part of the six hour bundle. Studies have shown delay in the initiation of vasopressor(s) contributes to poor outcomes. To date, there is no strong evidence supporting the superiority of one vasopressor over the others and no specific association with outcomes [9,12,18,23].

From routine day to day observation, septic shock is a common problem among patients at the University of Gondar Hospital. Neither the outcome of septic shock, nor the associated factors with poor outcomes, is known at the University of Gondar Hospital. Knowing the mortality rate of septic shock and sorting out specific factors associated with poor outcomes will help to improve the gap in the management of septic shock by allowing clinicians to practice evidence based medicine. This will be the first study to look at outcomes of septic shock and associated factors at the University of Gondar Hospital. According to the old sepsis definition, basics to the understanding of septic shock are defining systemic inflammatory response syndrome (SIRS) and sepsis. SIRS is diagnosed when a patient shows more than one of the following four clinical characteristics: {1} body temperature > 38°C or < 36°C; {2} heart rate > 90 beats/min; {3} hyperventilation, evidenced by a respiratory rate > 20 breaths/min or PaCO2 < 32 mmHg; and {4} white blood cell count > 12 000 cells/μL or < 4 000 cells/μL or with > 10% immature forms [1-3]. Sepsis is clinically appreciable when there is SIRS with suspected or evidenced microbial invasion. Severe sepsis is sepsis leading to variable degrees of organ dysfunction. Septic shock is severe sepsis with cardiovascular dysfunction manifesting with persistent arterial hypotension regardless of adequate fluid resuscitation [1,2,4]. Inline to the most recent sepsis 3 definition, Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction is represented by an increase in the Sepsis related-Organ Failure Assessment (SOFA) score of 2 points or more (Alteration in mental status, Decrease in systolic blood pressure of less than 100 mmHg, and Respiration rate greater than 22 breaths/min). Septic shock is defined as a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a higher risk of mortality. Patients with septic shock can clinically be identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia [5].

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Methods

Study design

Hospital based retrospective cohort study with record review of patients admitted with the diagnosis of septic shock from January 2014 to October 2016.

Study setting

The study was conducted at the University of Gondar Hospital, which is a teaching hospital located at Gondar city in Amhara region, Northwest Ethiopia. The hospital serves more than 5 million people from the city and adjacent catchment areas. Being the only tertiary hospital in Central Gondar zone; the burden of complicated cases requiring advanced care is significant. The division of internal medicine has an emergency department, three medical wards, MDR TB and VL treatment centers with a total of nearly a hundred beds and a MICU with four beds. Most patients with the diagnosis of septic shock are admitted to the MICU but due to the limited number of beds, a significant number of patients are treated either in the emergency department or in the general wards.

Study population

Adult patients admitted to the University of Gondar Hospital, Department of Internal Medicine with the diagnosis of septic shock from January 2014 to October 2016.

Inclusion criteria

- ✓ Age ≥ 18 years
- ✓ Admission diagnosis with septic shock

Exclusion criteria

- ✓ Final diagnosis cardiogenic shock
- ✓ Medical records with incomplete data

Variables

Independent variables

- ✓ Age
- ✓ Duration of illness
- ✓ Underlying medical disorder(s)
- ✓ Type of vasopressor used
- ✓ Sepsis related organ dysfunction
- ✓ Duration of hospital stay
- ✓ Steroid use

Outcome variable

- ✓ Death

Operational definition

Septic shock- Fluid unresponsive hypotension with BP < 90/60

Normothermia - Axillary Temperature 36.5 - 37.2°c

Hyperthermia - Axillary Temperature ≥37.2°c

Hypothermia - Axillary Temperature ≤36.5°c

Leucopenia - white cell count <5000/ul

Leukocytosis - white cell count >10,000/ul

Data collection procedure

Data collection instrument

Data was collected using a pretested structured questionnaire. Data collection was done by clinicians working in the hospital and trained on data collection. Cases were selected using the department's log book and medical records were retrieved from the hospital archives. There were 168 cases of septic shock recorded on the log book. Only the medical records of 121 patients could be retrieved. Out of the 121 cases, the outcome was not known for 16 cases, and 7 cases were patients who had sepsis without septic shock. Analysis was done for the remaining 98 cases of septic shock.

Data management and analysis

After checking for completeness, data entry was done using SPSS software version 20. Both descriptive and analytic statistical analysis was performed using SPSS software version 20. The Crude odds ratio was calculated for each independent variable and adjusted odds ratio using multiple regressions was calculated for those variables with P values less than 0.2 by binary regression. P-value less than 0.05 with 95% confidence interval is considered as a significant association between the independent variable and the outcome variable.

Results

Base line characteristics

The study was conducted among adult patients admitted to the University of Gondar Hospital with the diagnosis of septic shock from January 2014 to October 2016. Out of the 168 cases of septic shock identified, only 98 cases fulfilled the criteria to be included in this study. From the total of 98 cases, females accounted for 57% and the remaining 43% were males (**Table 1**).

The median duration of illness before presentation was 7 days (Interquartile Range- 11 days). The median for duration of hospital stay before the development of the outcome variables was 4 days (Interquartile Range-6 days).

Of the 98 cases, two thirds had fever or hypothermia as initial presentation. From those whose initial complete blood cell counts were examined, 75% had either leukocytosis or leucopenia. The gastrointestinal tract was the most common focus of primary infection followed by urinary tract (**Table 1**). Most of the patients had one or more co-morbidities identified during admission (60%) and the most common being HIV infection (52.5%). Most of them (Nearly 60%) received adrenalin as a vasopressor. Hydrocortisone was also given to 60% of the cases. Out of the 98 cases, 41 patients were discharged after they recovered from the septic shock. The in Hospital mortality rate of septic shock from this study is 44% (43 of 98 patients have died). Fourteen patients have gone against medical advice. Taking into account both the in Hospital deaths (44%) and those who went against medical advice (14%), 58% of septic shock patients had unfavorable outcome.

A third of the cases had sepsis related organ dysfunctions (33%), the most common being renal failure.

Factors associated with septic shock outcome

All covariates were checked against the dependent variable (mortality) for a significant association but only duration of illness before presentation, duration of hospital stay, presence of co-morbidities, steroid use and development of sepsis related organ dysfunctions met the criteria for multivariate analysis(P-value <0.2). On the contrary, age of the patient, sex, focus of infection, and type of vasopressor used failed to meet the criteria for multiple logistic regressions analysis.

Those septic shock patients with co-morbidities (AOR 4.7, P-value 0.02) and those with the diagnosis of refractory septic shock receiving steroids (AOR 17.5, P-value 0.001) are likely to die in hospital. A longer the duration of illness was associated with a higher risk of adverse outcomes from septic shock i.e. death and going home against medical advice (P-value 0.005) (The association of the various variable with septic shock treatment outcome is depicted in **Table 2** below).

Table 1 Baseline characteristics.

Variables	Value	Percent (%)
Sex		
Males	42	42.9
Females	56	57.1
Age category		
14-25	14	14.3
26-50	51	52
≥51	33	33.7
Temperature		
Normothermia	34	34.7
Hyperthermia	32	32.7
Hypothermia	32	32.7
Initial WBC		
Normal	24	24.5
Leukocytosis	40	40.8
Leucopenia	20	20.4
Unknown	14	14.3
Primary focus of infection		
Gastrointestinal	60	61.2
Respiratory	30	30.6
Urinary	5	5.1
Others	2	2
Unknown	1	1
Sepsis related organ dysfunction		
No	65	66.3
Renal	19	19.4
Respiratory	4	4.1
Hepatic	2	2
Multi-organ failure	8	8.2
Type of vasopressor used		
Adrenalin	60	61.2
Dopamine	36	36.7
Both	2	2
Steroid use		
Yes	59	60.2
No	39	39.8
Blood component transfusion		
Yes	15	15.3
No	83	84.7
Outcome		
Discharged improved	41	42
Went against medical advise	14	14
Dead	43	44
Co-morbidities		
No	39	39.8
HIV	31	31.6
Malignancies	7	7.1
Stroke	4	4.1
Heart failure	3	3.1
COPD	3	3.1
CKD	3	3.1
DM	2	2
VL	2	2
CLD	1	1
Multiple co-morbidities	1	1
Others	2	2

Table 2 Univariate and multivariate analysis.

Variables	UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
	COR	P-value	95% CI for the COR	AOR	P-value	95% CI for the AOR
Age						
14-25	1	0.9				
26-50	0.73	0.6	0.2-2.5			
>50	0.75	0.7	0.2-2.7			
Sex						
Male	1	0.7				
Female	1.3	0.5	0.6-3			
Duration of illness (days)						
1-7					**0.005**	
8-15	1		1-10	1	-	-
16-30	3.4	0.03	1-31	16	0.003	2.5-100
>30	6.4	0.02	0.3-37	26	0.002	3.2-200
	3.5	0.3		1.1	0.9	0.07-16
Duration of hospitalization (days)						
0-1					**0.002**	
2-7	-	0.05	0-	2	0.9	0-
8-15	-	0.9	0-	-	0.9	0-
>15	-	0.9	0-	-	0.9	0-
	1			1	-	-
Primary focus of infection						
GI						
Respiratory	1	0.2	1-9			
Renal	3	0.02	0.2-11			
Others	1.6	0.6	-			
Unknown	-	0.9	-			
	0.0001	1				
Types of vasopressor						
Adrenalin	0	0.98	0-			
Dopamine	0	0.99	0-			
Both	1					
Steroid use						
Yes	2	0.05	0.99-5	17.5	**0.001**	3-98
No	1			1		
Transfusion						
Yes	0.5	0.45	0.4-5			
No	1					
Co-morbidities						
Yes	2.3	0.06	0.98-5.1	4.7	**0.02**	1-17
No	1			1		
Organ dysfunction						
Yes	2.5	0.05	1-6	1.3		
No	1			1	0.74	0.3-5

Discussion

The In-hospital mortality rate of septic shock from this study is very high (42%). The unfavorable outcome of septic shock, the sum of the In-hospital death with those who went against medical advice, is 58%. This finding is consistent with older studies but higher than recent ones. The higher mortality rate of septic shock from this study can be explained by the inherent nature of the disease (30-50% mortality from different literatures), the relatively large number of patients with preexisting co-morbidities, and the higher rates of patients who went against medical advice (14%). The absence of customized hospital based protocols for early identification and management of septic shock may also have contributed to the higher mortality. In addition to limited knowledge and resources, the mortality of septic shock in low and middle income countries is believed to be disproportionately high due to widespread malnutrition, and higher rates of bacterial, parasitic, and HIV infection. HIV was found in 32% of the cases in this study and thus, contributed to the higher mortality rate [2,7,13-16,24].

Compared to studies conducted in the West where septic shock tends to occur more in the elderly, this study found middle aged individuals are more (52%) affected by septic shock. This can be explained by the difference The In-hospital mortality rate of septic shock from this study is very high (42%). The unfavorable outcome of septic shock, the sum of the In-hospital death with those who went against medical advice, is 58%. This finding is consistent with older studies but higher than recent ones. The higher mortality rate of septic shock from this study can be explained

by the inherent nature of the disease (30-50% mortality from different literatures), the relatively large number of patients with preexisting co-morbidities, and the higher rates of patients who went against medical advice (14%). The absence of customized hospital based protocols for early identification and management of septic shock may also have contributed to the higher mortality. In addition to limited knowledge and resources, the mortality of septic shock in low and middle income countries is believed to be disproportionately high due to widespread malnutrition, and higher rates of bacterial, parasitic, and HIV infection. HIV was found in 32% of the cases in this study and thus, contributed to the higher mortality rate [2,7,13-16,24].

Compared to studies conducted in the West where septic shock tends to occur more in the elderly, this study found middle aged individuals are more(52%) affected by septic shock. This can be explained by the difference in the underlying co-morbid conditions predisposing to septic shock. Cancers and diabetes mellitus, which are very common among elderly patients, account for the greater share of the co-morbidities in the developed world as opposed to HIV infection in this study in particular and the third world in general [1,8,9,13].

Gastrointestinal tract (61%) was the most common primary focus of infection leading to septic shock followed by respiratory tract (30%) and urinary tract accounting only for 5% of the primary focus. This is in contrary to some studies in developed nations which showed higher values for respiratory tract and urinary tract. This again is probably related to the difference in the study populations and the preexisting co-morbidities [11,20].

In this study, 60% of patients received corticosteroids, and there was statistically significant association between steroid use and mortality (AOR-17.5, P-value 0.001). The higher number of patients who received steroids indirectly indicates the burden of refractory septic shock not responding to fluid and vasopressor therapy alone. The literature shows steroids use increases mortality. The benefits of steroids in patients experiencing septic shock is limited only to refractory cases not responding to fluid and vasopressor therapy [7,11,12,24].

Similar to studies done by Backer, D. D. et al. and Patel, G. P. & Balk, R. A., this study shows no statistical difference in mortality with regard to the type of vasopressor used. This study compared the use of adrenalin and dopamine. The former studies compared adrenalin (epinephrine) versus norepinephrine and dopamine versus norepinephrine. Despite the differences in the occurrence of some adverse effects, these studies didn't show any mortality difference between the different vasopressor groups. Different studies have shown the negative effect of delayed initiation of vasopressor in determining outcome of septic shock.

Due to the retrospective nature of this study, it was not possible to demonstrate the association between timing of vasopressor therapy and mortality [5,6,19,22].

Different literatures has shown that the presence of specific sepsis related organ dysfunction significantly increases septic shock related mortality [1,2,17,24]. Similarly, this study also showed statistically significant association between sepsis related organ dysfunction and mortality with binary logistic regression (P value-0.047, COR - 2.53). But the association was not statistically significant with multiple logistic regressions. This is likely to be the effect of the small sample size.

In line with other studies, this study showed significant and strong association between the presence of preexisting co-morbid medical conditions and mortality associated with septic shock (P-value-0.02, AOR-4.7) [7,11,24].

This study also showed significant association between mortality of septic shock and duration of illness and hospitalization. Longer the duration of illness was associated with a higher mortality (P value 0.005). On the other hand, a longer the duration of hospital stay was associated with a lower the mortality rate (P-value -0.002). The lower mortality with prolonged stay can be explained by the fact that most mortalities in septic shock occur during the early hours or days of admission. This finding emphasizes the significant role of early identification and treatment of septic shock [12,15,17].

Strength and Limitation of the Study

This is the first study in Ethiopia that was concerned mainly on septic shock treatment outcome thus giving important knowledge on this important medical emergency. The other strength of this study is that the cohort design of the study.

This study has the following limitations. One of the limitations is the relatively small sample size. The other limitation of this study is its retrospective nature. Similarly the patients who went against medical advice and the incomplete records might have negatively affected our results.

Conclusion and Recommendations

Septic shock has high mortality in Gondar, Ethiopia, where nearly half of the patients had died. Strategies shall be paved to let patients with possible septic shock visit health facilities early and patients with co-morbidities need a more vigilant care.

Declaration

Ethical approval

Ethical clearance was obtained from the review board of the College of Medicine and Health Sciences, University of Gondar ((INM/319/12/08). Formal permission was also obtained from the Department of Internal Medicine and the office of the Clinical Director office. The requirement for consent has been waived by the ethics committee as this was done retrospectively. All data collected was maintained per the institutional privacy and confidentiality guidelines.

Consent for application

Not applicable

Availability of data and materials

The data sets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no financial or non-financial competing interests.

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Authors' contribution

FE, YG, ZA, SA were involved in data collection. HS, TY, OA, ES, TM were involved in data analysis, interpretation and final writing. All authors read and approved the final manuscript.

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