Original Article

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Factors Associated with Severe Sepsis or Septic Shock in Patients with Gram Negative Bacteraemia: An Observational Cohort Study

Internal Medicine Section

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ABSTRACT

Introduction: Sepsis is a systemic, host response to infection that progresses from sepsis to severe sepsis to septic shock. Severe sepsis carries significant morbidity and mortality. In the presence of individual risk factors such as old age, diabetes mellitus, chronic liver and renal disease, the death rate remains high despite treatment with antimicrobial agents.

Aim: To determine the factors associated with severe sepsis or septic shock and to identify the factors influencing the mortality among patients with gram-negative bacteraemia.

Materials and Methods: In this observational cohort study, 219 patients with gram-negative bacteraemia were screened for the presence of sepsis, severe sepsis and septic shock and detailed characteristics of the patients were analysed using independent sample t-test, chi-square test and logistic regression.

Results: Among 219 patients with gram-negative bacteraemia, 43 (19.6%) were classified as severe sepsis, 69 (31.5%) as septic shock and the remaining 107 (48.9%) as only sepsis according to clinical criteria. Diabetes mellitus (p-value=0.006), chronic liver disease (p-value=0.001), presence of urinary catheter (p-value<0.001) and organisms other than *E. coli* (p-value=0.036) had a significant association with severe sepsis. Mortality was observed in 82 (73.3%) patients with severe sepsis and septic shock. The factors that predicted mortality among patients with gram-negative bacteraemia were age ≥65 years, chronic liver disease, indwelling urinary catheter, endotracheal and nasogastric tube, central venous access, organisms other than *E. coli*, respiratory and abdominal sources of infection. The mean Pitt bacteraemia score of >4 was significant (p-value <0.001) for development of severe sepsis and septic shock and mortality was higher in those with high scores. (p-value <0.0001).

Conclusion: The present findings suggest that diabetes mellitus, chronic liver disease, indwelling urinary catheter and organisms other than *E. coli* are important risk factors for the development of severe sepsis or septic shock. Patients with higher Pitt bacteraemia score may have higher risk of death.

Keywords: Gram-negative bacilli, Pitt bacteraemia score, Risk factors

INTRODUCTION

Sepsis is dysregulated and uncontrolled inflammatory response to infection [1]. The presence of severe sepsis due to gram-negative bacteraemia is an increasingly common cause of morbidity and mortality in developing countries. The mortality is much higher in patients with severe sepsis than that with sepsis and the limited development of antimicrobial agents against gram-negative bacilli has made the treatment more difficult [2].

The increased incidence of infections due to gram-negative bacilli is of great concern in recent years, as patients infected by such isolates might initially receive inappropriate antibiotics against the responsible pathogens. Furthermore, in the presence of underlying comorbidities and organ dysfunction, the mortality is still high among patients with severe sepsis and septic shock [3,4]. The presence of severe sepsis is often missed by the clinicians, even when organ dysfunction is present. Recent evidence suggests that early diagnosis with prompt and accurate initiation of treatment has shown significant improvement in the outcome of patient [5-7].

The factors predicting severe sepsis and septic shock have been well described in the previous studies in different countries [8-10]. However, studies concerning the same among Indian population are limited with varying results in view of increased occurrence of gram-negative infections. Hence, this study was undertaken to evaluate factors associated with severe sepsis or septic shock and to identify the factors influencing the mortality among patients with gram-negative bacteraemia.

MATERIALS AND METHODS

This observational cohort study was conducted on patients aged 18 years and above admitted to medical wards or Intensive Care Units between September 2013 and August 2015 at a Tertiary Hospital in Southern India. This study was approved by the Institutional Ethics Committee (IEC 520/2013).

Inclusion criteria: Patients with clinical suspicion of sepsis, supported by blood culture with at least one positive culture showing single type of gram-negative bacilli were included.

Exclusion criteria: Patients with blood culture growing both gram negative and gram-positive organism, those with blood culture positive for two types of gram-negative bacilli or those with blood culture positive for *Salmonella typhi* or *Brucella* species were excluded from the study. Patients who required immediate surgical intervention were also excluded.

After obtaining written consent, patients with positive blood culture for gram-negative bacteria were selected on the first day of being diagnosed with infection. The data elements such as age, gender, presence of comorbid condition, source of infection and pathogens isolated from blood cultures were recorded. The presence of comorbidities including diabetes mellitus, acquisition of nosocomial infection, associated chronic kidney and liver disease, chronic obstructive pulmonary disease, retroviral disease, malignancy and systemic steroid use was documented. The presence of urinary catheter, tube insertions (endotracheal or nasogastric), central venous access was also noted provided they were in-situ for at least 48 hours prior to the day on which

blood culture was drawn. The severity of illness in the form of Pitt Bacteraemia Score (PBS) [11] was calculated for all the patients in the study group.

Sepsis, severe sepsis and septic shock were diagnosed using American College of Chest Physicians/Society of Critical Care Medicine consensus conference definitions [1]. Infections which occurred after 48 hours of admission into hospital were considered as nosocomial infections while those which occurred within 48 hours of admission were considered community-acquired infection [12]. PBS which includes five variables namely oral temperature, hypotension, mechanical ventilation, cardiac arrest and mental status was calculated and graded within 48 hours before or on the day of first positive blood culture. A score of >4 indicates that patient has severe illness [11].

STATISTICAL ANALYSIS

Statistical analyses were carried out using SPSS version 15. The sample size was based on the comparison of exposure to chronic liver disease or chronic kidney disease among sepsis and severe sepsis. Assuming 40% and 60% of exposure among both groups, the minimum sample size required was 95 in each group at 5% level of significance and 80% power. The study was continued till the end of study period and the total number of patients recruited was 219. Mean±SD was used to summarise continuous variables. All categorical variables were summarised using frequency and percentages. Independent sample t-test was used to compare mean of continuous variables among patients with sepsis, severe sepsis and septic shock. Chi-square test was used as a test of association between categorical variables. A stepwise logistic regression analysis was used to find significant factors associated with severe sepsis and septic shock. Odds ratio with 95% confidence interval was used as strength of association. Relative risk with 95% confidence interval was used as strength of association for mortality across categorical exposure variables. All tests of significance were two-tailed and a p-value of <0.05 was considered as statistically significant.

RESULTS

A total of 219 patients with a mean age of 51.9±15.4 years were included in the study. There were 174 (79.5%) males and 45 (20.5%) females with a male to female ratio of 3.87:1. Of the 219 patients with gram-negative bacteraemia, 69 (31.5%) had septic shock, 43 (19.6%) had severe sepsis and the remaining 107 (48.9%) had only sepsis. The most common underlying risk factors associated with the severity of sepsis were age ≥65years (20.5%), diabetes mellitus (53.9%), chronic liver disease (34.2%), presence of urinary catheter (29.7%) and nasogastric tube (29.7%) [Table/Fig-1].

The predominant blood culture isolates were *Escherichia coli* (n=120, 54.8%) followed by *Klebsiella pneumonia* (n=56, 25.6%), *Acinetobacter baumannii* (n=19, 8.7%), *Pseudomonas aeruginosa* (n=17, 7.8%) and *Enterobacter* species (n=7, 3.2%). Most of the isolates were obtained from the urinary tract (n=101, 46.1%) followed by respiratory tract (n=50, 22.8%) and abdomen (n=40, 18%). Eighteen patients (8.2%) had primary bacteraemia where the definite source of infection was not identified. The distribution of microorganisms and the source of infection has been summarised in [Table/Fig-2]. When microorganisms were analysed with respect to the source of infection as a risk factor, it was found that *E. coli* with abdominal source of bacteraemia had a statistically significant association with severe sepsis and septic shock (OR=3.97, 95%; CI=1.44-11.6), though *E. coli* was not found to have statistical significance as a whole. Retroviral disease could not be included in analysis as there were only three patients who had satisfied all the criteria for this study and none of them was in sepsis group.

Variable	Severe sepsis or setic shock (n=112)	Sepsis (n=107)	p-value	Unadjusted OR (95% CI)
Age ≥65 years	29 (25.9)	16 (15.0)	**0.045**	1.98 (1.10-4.20)
Prior Hospitalisation	52 (46.4)	39 (36.4)	0.134	1.51 (0.85-2.69)
Diabetes Mellitus	69 (61.6)	49 (45.8)	**0.019**	1.90 (1.10-3.37)
Acquisition of nosocomial infection	29 (25.9)	14 (13.1)	**0.017**	2.32 (1.10-5.07)
Chronic kidney disease	17 (15.2)	20 (18.7)	0.488	0.77 (0.35-1.67)
Chronic liver disease	49 (43.8)	26 (24.3)	**0.002**	2.42 (1.31-4.52)
COPD	9 (8.0)	6 (5.6)	0.477	1.47 (0.45-5.21)
Haematologic malignancy	5 (4.5)	1 (0.9)	0.110	4.95 (0.5-236.4)
Solid malignancy	3 (2.7)	6 (5.6)	0.275	0.46 (0.07-2.24)
Systemic steroids	3 (2.7)	4 (3.7)	0.656	0.71 (0.10-1.30)
Indwelling urinary catheter	56 (50.0)	9 (8.4)	**<0.001**	10.8 (4.82-26.7)
Endotracheal tube	55 (49.1)	1 (0.9)	**<0.001**	102 (16.3-4149.2)
Nasogastric tube	62 (55.4)	3 (2.8)	**<0.001**	42.9 (12.8-220.6)
Central venous access	27 (24.1)	3 (2.8)	**<0.001**	11.01 (3.19-58.11)
Pitt bacteraemia score (mean±standard deviation)	4.63±1.10	1.12±1.00	**<0.001**	

[Table/Fig-1]: Clinical characteristics and univariate analysis to evaluate for risk factors for development of severe sepsis or septic shock in patients with gram negative bacteraemia.
COPD: Chronic obstructive pulmonary disease

	Severe sepsis/septic shock (n=111)	sepsis (n=107)	Unadjusted OR (95% CI)
Microorganism			
Escherichia coli	52 (46.4)	68 (63.6)	0.50 (0.28-0.88)
Acinetobacter baumanii	16 (14.3)	3 (2.8)	5.77 (1.57-31.67)
Enterobacter spp	2 (1.8)	5 (4.7)	0.37 (0.03-2.34)
Klebsiella Pneumoniae	35 (31.2)	21 (19.6)	1.86 (0.95-3.66)
Pseudomonas aeruginosa	7 (6.2)	10 (9.3)	0.65 (0.2-1.97)
Source of infection			
Urinary tract	36 (32.1)	65 (60.7)	0.31 (0.17-0.55)
Respiratory tract	37 (33.0)	13 (12.1)	3.57 (1.70-7.82)
Abdomen	27 (24.1)	13 (12.1)	2.29 (1.1-5.16)
CRBSI	7 (6.2)	3 (2.8)	5.64 (1.54-31.02)
Unknown source	5 (4.5)	13 (12.1)	0.34 (0.091-1.06)

[Table/Fig-2]: Distribution of microorganisms and source of infection.
CRBSI: Central line related blood stream infection

A stepwise logistic regression analysis was used to identify significant factors associated with severe sepsis. Presence of endotracheal tube, nasogastric tube, central venous access and associated retro-viral disease could not be included in the analysis as the number of patients in sepsis group was <5. [Table/Fig-3] shows factors found to have independent association with severe sepsis and septic shock among patients with gram-negative bacteraemia.

Variable	p-value	Adjusted OR (95% CI)
Diabetes mellitus	0.006	2.55 (1.31-4.94)
Chronic liver disease	0.001	3.45 (1.71-6.97)
Indwelling urinary catheter	<0.001	15.01 (5.72-39.37)
Organisms other than *E. Coli*	0.036	2.06 (1.10-4.07)

[Table/Fig-3]: Independent risk factors associated with development of severe sepsis or septic shock (adjusted OR) in patients with gram negative bacteraemia.
OR: Odds ratio; CI: Confidence interval; *E. Coli: Escherichia coli*

Mortality occurred in 13 (12.1%) patients with only sepsis and in 82 (73.3%) with severe sepsis and septic shock which was

significantly higher. The factors that predicted mortality among patients with gram-negative bacteraemia were age ≥65 years (RR=6.02, 95%; CI=1.10-1.81), chronic liver disease (RR=2.04, 95%;CI=1.53-2.73), presence of urinary catheter (RR=2.13, 95%; CI=1.61-2.82), endotracheal tube (RR=2.61, 95%; CI=2.01-3.41), nasogastric tube (RR=2.84, 95%;CI=2.14-3.78), central venous access (RR=1.68, 95%; CI=1.27-2.28), organisms other than *E. coli* (RR=1.67, 95%; CI=1.23-2.27), respiratory (RR=1.97, 95%;CI=1.50-2.59) and abdominal (RR=1.77, 95%;CI=1.34-2.36) sources of infection. The mean PBS of >4 was significant for development of severe sepsis and septic shock and also that mortality was higher in those with high scores [Table/Fig-4].

Variable	Non-Survivors (n=95)	Survivors (n=124)	RR (95% CI)	p-value
Age ≥65 years	26 (64.4)	19 (35.6)	1.41 (1.10-1.81)	0.043
Prior Hospitalisation	43 (47.3)	48 (52.7)	1.16 (0.86-1.57)	0.403
Diabetes Mellitus	52 (44.1)	66 (55.9)	1.03 (0.76-1.40)	0.932
Acquisition of nosocomial infection	22 (51.2)	21 (48.8)	1.2 (0.87-1.73)	0.328
Chronic kidney disease	13 (35.1)	24 (64.9)	0.78 (0.49-1.24)	0.353
Chronic liver disease	49 (65.3)	26 (34.7)	2.04 (1.53-2.73)	<0.0001
COPD	7 (46.7)	8 (53.3)	1.08 (0.62-1.90)	1
Haematologic malignancy	5 (83.3)	1 (16.7)	1.97 (1.33-2.91)	0.113
Solid malignancy	6 (66.7)	3 (33.3)	1.57 (0.97-2.57)	0.273
Systemic steroids	3 (42.9)	4 (57.1)	0.98 (0.41-2.36)	1
Indwelling urinary catheter	45 (69.2)	20 (30.8)	2.13 (1.61-2.82)	<0.0001
Endotracheal tube	45 (80.4)	11 (19.6)	2.61 (2.01-3.41)	<0.0001
Nasogastric tube	52 (80.0)	13 (20.0)	2.84 (2.14- 3.78)	<0.0001
Central venous access	20 (66.7)	10 (33.3)	1.68 (1.23-2.28)	0.010
Organisms other than *E. coli*	55 (55.5)	44 (44,5)	1.67 (1.23-2.27)	0.0015
Urinary tract infection	24 (23.8)	77 (76.2)	0.39 (0.27-0.57)	<0.0001
Respiratory tract infection	35 (70.0)	15 (30.0)	1.97 (1.50-2.59)	<0.0001
Abdominal infection	27 (67.5)	13 (32.5)	1.77 (1.34-2.36)	0.00125
CRBSI	3 (30.0)	7 (70.0)	0.68 (0.26-1.78)	0.584
Unknown source	6 (33.3)	12 (66.7)	0.75 (0.38-1.47)	0.516
Pitt bacteraemia score (mean±standard deviation)	4.64±1.24	1.59±1.49		<0.0001

[Table/Fig-4]: Factors associated with mortality in patients with gram negative bacteraemia.
COPD: Chronic obstructive pulmonary disease; CRBSI: Central line related bloodstream infection

DISCUSSION

In the present study, it was observed that 51.1% cases presented with severe sepsis and septic shock, which was high compared to recent studies in gram-negative bacteraemia by Kang CI et al., (22.1%) and Mayr FB et al., (30%) [2,13]. The higher rate of severe sepsis and septic shock in this study may be because majority of patients are brought or referred to present tertiary hospital mostly when the infection is not responding to common treatment and there is a delay in time of presentation to the centre from the onset of infection.

Acquisition of nosocomial infections due to the presence of urinary catheter, endotracheal and nasogastric tube and central venous access were identified as risk factors for severe sepsis in the present study. Multivariate analysis demonstrated indwelling urinary catheter as the significant independent risk factor for severe sepsis. This finding implies that the severity of sepsis due to gram-negative bacteria can be reduced by minimising the insertion of indwelling catheters to the maximum extent as possible [2]. Formation of biofilms over the indwelling catheters and lines is one of the important reasons for persistence of microbes despite treating the patient with sensitive antibiotics and thus poses an important risk factor for severe sepsis [14].

No specific underlying disease except for chronic liver disease in the study was evidently associated with severe sepsis which contributed to increased mortality rate. It is emphasised that presence of cirrhosis significantly influences the function of neutrophils, monocytes, macrophages and lymphocytes with defective opsonisation leading to immune dysfunction. Furthermore, reticuloendothelial cells in the liver are important for clearing bacteria and portosystemic shunting of blood allows fewer bacteria and endotoxins to be cleared by liver and thus patients with chronic liver disease are more prone to develop severe illness and have higher mortality [15]. Authors also observed that patients with diabetes mellitus were prone to develop severe sepsis which was in accordance with study conducted by Kang CI et al., [2]. These findings suggest that host factors are frequently responsible for the development of severe sepsis and hence, antibiotic treatment should be started as early as possible awaiting culture reports.

Though urinary tract was the most frequent source of bacteraemia, urinary, lung and abdominal sources of infections were not found to be statistically significant for the development of severe sepsis after adjusting for confounding variables. However, respiratory and abdominal source of infections accounted for higher mortality which is similar to a previous study by Zilberberg MD et al., which found that respiratory tract and abdomen were the most common sources of infection with significant association with gram-negative sepsis and shock with high mortality [16]. Similar to previous studies [2,17], authors found that *E. coli* was the most frequently detected microorganism in the present series. However, infection with gram- negative bacteria other than *E. coli* were found to be significant risk factor for the development of severe sepsis and also for increased mortality.

It was observed that patients with severe sepsis or septic shock had a higher mortality rate (73.3%) than those without severe sepsis or shock (12.1%) however, no significant difference in mortality was observed among those with severe sepsis (69.8%) and septic shock (75.4%). This is in contrast to a previous study by Kang CI et al., which reported that the mortality was significantly higher among patients with septic shock than that of patients with severe sepsis (48.6% vs. 22.1%) [2]. The present study demonstrated that patients with high PBS were at increased risk of developing severe sepsis with high mortality which is in agreement with recent studies conducted by Feldman C et al., and Rhee JY et al., with regard to scoring systems, showed similar results and also observed that PBS was superior to APACHE II score with respect to gram-negative bacteraemia in predicting severe illness [18,19].

LIMITATION

This study had few limitations such as inability to assess patients with certain risk factors like associated malignancy, who are not frequently admitted under medicine department. Also, patients were categorised on the first day of being diagnosed as having gram-negative bacteraemia depending upon the degree of septic response. However, assessment of patients at a single point of time could be a limitation of this study since patients could have developed severe sepsis or septic shock during the course of the illness.

CONCLUSION

Presence of urinary catheter, comorbidities such as diabetes mellitus and chronic liver disease and organisms other than *E. coli* were the most important independent risk factors for the development of severe sepsis and septic shock in patients with gram-negative bacteraemia. Factors contributing to mortality included age ≥65 years, chronic liver disease, urinary catheter, endotracheal and nasogastric tube, central venous access, organisms other than *E. coli*, respiratory and abdominal sources of infection and higher Pitt Bacteraemia Score (PBS). It is important for the clinicians to identify high-risk patient groups prone to developing severe sepsis in order to initiate timely and appropriate management.

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