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HOW EARLY DO ANTIBIOTICS HAVE TO BE TO IMPACT MORTALITY IN SEVERE SEPSIS? A PROSPECTIVE, OBSERVATIONAL STUDY FROM AN EMERGENCY DEPARTMENT

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Background: The objective of this study was to assess the promptness of antibiotic administration to patients presenting with sepsis and the effects on survival and length of hospitalization. **Methods:** Consecutive, adult patients presenting with Systemic Inflammatory Response Syndrome (SIRS) to the emergency department of the Aga Khan University hospital were enrolled in a prospective, observational study over a period of 4 months. Univariate, multivariate regression modeling and one-way ANOVA were used to examine the effects of various variables on survival and for significant differences between timing of antibiotic administration and survival, two-sided p values <0.05 were considered significant. **Results:** One hundred and eleven patients were enrolled. Severe sepsis was present in 52% patients; the most frequent organism isolated was Salmonella typhi (18%). Overall mortality was 35.1%. One hundred (90.1%) patients received intravenous antibiotics in the Emergency room; average time from triage to actual administration was 2.48±1.86 hours. The timing of antibiotic administration was significantly associated with survival (F statistic 2.17, p=0.003). Using a Cox Regression model, we were able to demonstrate that survival dropped acutely with every hourly delay in antibiotic administration. On multivariate analysis, use of vasopressors (adjusted OR 23.89, 95% CI 2.16,263, p=0.01) and Escherichia coli sepsis (adjusted OR 6.22, 95% CI 1.21,32, p=0.03) were adversely related with mortality. **Conclusions:** We demonstrated that in the population presenting to our emergency room, each hourly delay in antibiotic administration was associated with an increase in mortality.

Keywords: sepsis, shock, antibiotics, emergency department

INTRODUCTION

Severe sepsis and septic shock are common conditions that lead to hospitalisation. Though data from Pakistan is almost nonexistent, it is estimated that about 2.9% of hospital admissions and 10% of intensive care unit admissions are due to severe sepsis.[1,2] Also, perhaps more significantly, more than half of such cases initially present to the emergency department.[3]

Despite improvements in health care services, the mortality rate from severe sepsis and shock remains high exceeding 30% in the West and 60% in the developing world.[4,5] Initiating effective antibiotic therapies in severe sepsis and shock is proven to lead to better outcomes. The Surviving Sepsis Campaign[7] developed in 2004, incorporated evidence-based guidelines to reduce mortality from severe sepsis and septic shock. These include the early initiation of broad spectrum antimicrobials, i.e., within 1 hour of recognition of sepsis.

Unfortunately guidelines are not always immediately incorporated. There are delays in recognition of disease states and in institution of therapy, especially in the emergency room setting where patient volumes and time constraints put additional burdens on the care providers.[8]

The objective of this study was to assess the compliance with the Surviving Sepsis Guidelines in our Emergency department and the subsequent effects on length of hospitalisation and survival.

MATERIAL AND METHODS

This was a prospective, observational study that enrolled consecutive adult patients presenting with Systemic Inflammatory Response Syndrome to the emergency department of the Aga Khan University hospital. The study extended period from February–June 2008. Patient enrolment was by convenience sampling.

Systemic Inflammatory Response Syndrome (SIRS) was defined according to the criteria proscribed by the Society of Critical Care Medicine[9,10], i.e., patients presenting with any two clinical signs, tachypnoea, sinus tachycardia, body temperature <35 °C or >38 °C, white blood cell counts <4,000 or >10,000. Sepsis was defined as the presence of any 2 or more SIRS criteria in the setting of a documented or presumed infection. Severe sepsis was defined by concomitant organ dysfunction and Septic shock in the presence of accompanying sustained hypotension (<90 mm Hg systolic blood pressure or <65 mm Hg mean arterial pressure) despite adequate fluid resuscitation. Antibiotics were considered *appropriate* if on subsequent culture, the organism demonstrated in vitro sensitivity to that antibiotic.

A research officer stationed in the emergency room identified patients. Exclusion criteria were age

<18 years, patients transferred from other hospitals or chronic care facilities or those already receiving antibiotics. Demographic and study-specific data were collected. The patient was followed until either death or discharge.

The study protocol was approved by the Hospital Ethical Review Committee.

Continuous data is expressed as Mean±SD, categorical data is expressed as percentages. The primary outcome variable was survival to hospital discharge and the secondary outcome was length of hospitalisation. Univariate and multivariate regression modeling were used to examine the effects of various variables on survival. Chi-square test, or Fisher's exact test where appropriate, and one-way ANOVA were used to check for significant differences between timings of antibiotic administration and survival; two-sided $p<0.05$ were considered significant. All analyses were carried out using SPSS version 14.0.

RESULTS

One hundred and eleven patients were enrolled in the study; the average age was 69 years, 56% were males. All patients met criteria for SIRS at enrolment; sepsis was later confirmed by cultures in 96 (86.4%) patients. Fourteen patients (14.6%) were in shock. Figure-1 illustrates the distribution of patients according to severity of Sepsis or those in SIRS.

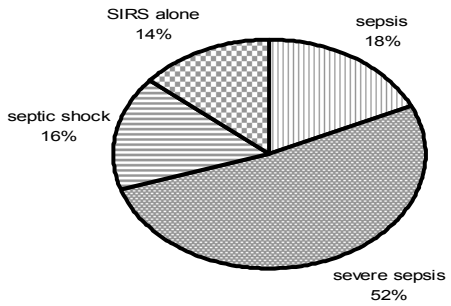

Figure-1: Distribution of patients with sepsis

The most common cause of sepsis, as shown in Table-1, was bloodstream infections in 65 patients (67.7%), followed by pneumonia in 21 (21.9%) and meningitis in 10 (10.4%). Salmonella typhi (17.7%) and Escherichia coli (12.5%) were the most frequent organisms isolated. Over 40% of the patients had no organism isolated on culture. Other organisms were; Staphylococcus, aureus (7%), Pneumococcus (6%), Klebsiella (5%), Pseudomonas aeruginosa (4.5%) candida albicans (3%).

One hundred (90.1%) patients received intravenous antibiotics in the Emergency Department (ED), the mean time from ED registration to actual administration was 2.48±1.86 hours. The most frequently administered antibiotic in the ED was Ceftriaxone (46.8%) followed by other cephalosporins (cefixime, cefipime) in 15.7%, fluroquinolones (ciprofloxacin, levofloxacin) in 13.5% and metronidazole, vancomycin, clindamycin together accounted for 14.7%. Ampicillin, cloxacillin, amoxicillin with beta lactamase inhibitors were used in only 6.6% and aminoglycosides in 2.7%. On subsequent culture reports, it was confirmed that 65 (67.7%) patients received appropriate antibiotics.

Of all the patients presenting with SIRS, only 62 (55.9%) received 1 litre or more of intravenous fluid resuscitation in less than 4 hours. Vasopressors were used in 14 (12.6%) patients. Overall mortality with Sepsis was 34.2% (38 patients), with a mean length of hospitalisation of 4.78±3.41 days (range <1–14 days).

Table-1: Types of organisms isolated from patients with sepsis

Organism	Frequency	Percent
Pneumococcus	6	5.4
Escherichia coli	14	12.6
Salmonella typhi	18	16.2
Klebsiella	5	4.5
Staphylococcus	7	6.3
Pseudomonas	4	3.6
Candida	4	3.6
Bacteroides	2	1.8
No growth	2	1.8

The timing of antibiotic administration was significantly associated with survival (F statistic 2.17, $p=0.003$). Using a Cox Regression model, we were able to demonstrate that survival dropped acutely with every hourly delay in antibiotic administration (Figure-2).

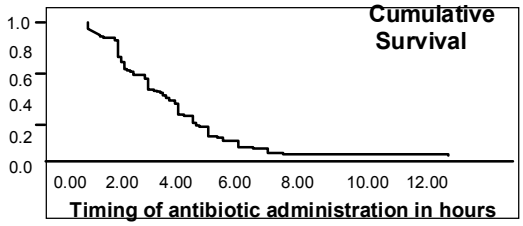

Figure-2: Cox regression model showing a drop in cumulative survival with delays in antibiotic administration

Table-2 shows the univariate regression analysis indicated significant associations between increased mortality and delayed antibiotic administration, need for vasopressors, Escherichia coli or Candida septicaemia and inability to receive greater than 1 litre fluid resuscitation within 4 hours of presentation to the emergency room. On multivariate analysis, as shown in Table-3, use of vasopressors (adjusted odds ratio 23.89, 2.16–263, $p=0.01$) and Escherichia coli sepsis (adjusted odds ratio 6.22, 1.21–32, $p=0.03$) were adversely related with mortality.

Table-2: Univariate analysis of risk factors for an increased in-hospital Mortality in patients presenting with Sepsis

Factor	Death (%) n=38	Discharge (%) n=73	Crude OR	95% CI	*p* value
Timing of Antibiotic administration	3 hrs±1.47	2.20±2 hours	0.79	0.63, 0.98	0.04
Length of hospitalisation	4.84 days±3.2	4.75±3.5 days	0.99	0.88, 1.14	0.89
Culture result					
Positive	28 (73.7)	42 (57.5)	0.48		
Negative	10 (26.3)	31 (42.5)	1.0	0.20, 1.14	0.09
IV fluids >1L within 4 hours					
Yes	30 (78.9)	32 (43.8)	0.20		
No	8 (21.1)	41 (56.2)	1.0	0.08, 0.51	0.001
Appropriate antibiotics given					
Yes	37 (97.4)	63 (86.3)			
No	1 (2.6)	10 (13.7)	0.17	0.02, 1.38	0.09
Vasopressors used					
Yes	12 (31.6)	2 (2.7)			
No	26 (68.4)	71 (97.3)	0.06	0.01, 0.29	<0.001
Escherichia coli sepsis	11 (78.5%)	3 (21.4%)	15.03	3.52 , 64	<0.000
Candida sepsis	3 (75%)	1 (25%)	12.3	1.15 , 131	0.03

Table-3: Multivariate logistic regression model of factors associated with an increased likelihood of survival to hospital discharge in patients with Sepsis

Characteristics	Adjusted OR	95% CI	*p*
Timing of Antibiotic administration	0.84	0.65, 1.08	0.18
IV fluids >1L within 4 hours			
Yes	0.24	0.09, 0.65	0.005
No	1.0		
Vasopressors			
Used	0.07	0.01, 0.37	0.002
Not used			

-2 log likelihood=112.572, p=0.95

Mortality in the subgroup that presented with Septic shock was 100%; 37.5% of patients presented with septicaemia alone whilst 25% patients had a pre-existing pneumonia. The most frequent organism isolated was Escherichia coli (37.5%) followed by Salmonella typhi (31.3%) and pseudomonas (12.5%). Only 62.5% patients received appropriate antibiotics as proved by subsequent cultures. Average time for antibiotic administration was 3.63±1.44 hours. The majority of patients received appropriate aggressive resuscitative care; 100% received antibiotics and 81% greater than 1 litre of intravenous fluids within 4 hours of presentation. However, only 50% received vasopressor support in the emergency room.

DISCUSSION

Our results show that the earlier an appropriate antibiotic is administered, the better the chances for survival in sepsis. We demonstrated that in the population presenting to our emergency room, each hourly delay in antibiotic administration was associated with an increase in mortality.

The biggest challenge in sepsis is early recognition of the problem. The presentation of severe sepsis and septic shock can initially be non-specific, but can progress within hours to fulminant multiple organ failure and death.[11] Patients presenting to the emergency department with sepsis may not receive timely or appropriate antibiotics since the diagnoses of systemic inflammatory response syndrome (SIRS) as well as sepsis are often missed.[12] Delays in the identification, transfer and management of critically ill patients during the first 6 hours after admission have been associated with higher mortality rates[13] and increased utilisation of hospital resources[14]. Antimicrobial selection is often random and erratic. Delaying antibiotic administration maybe related to worsened clinical outcomes.[15] Patients eventually arrive in the intensive care unit in a moribund state with profound shock and multi-organ failure.[16,17]

Better understanding of the pathophysiology of sepsis has led to recommendations which target both early and goal-directed management to improve outcomes.[18] The timeliness of treatment became apparent after Rivers *et al*[19] showed a significant mortality benefit when heamodynamic optimization was provided within the first few hours of disease presentation. These ideals have been incorporated into the Surviving Sepsis Campaign, a multinational initiative, which recommends a 24-hour sepsis pathway that includes a critical 6-hour course of action.[7]

Results of studies from predominantly Europe and North America document the mortality and morbidity benefits of both early and appropriate antimicrobials.[20,21,24–26] Kollef *et al*[20] in their landmark paper on 2000 patients with both community-acquired and nosocomial infections, demonstrated that inadequate antimicrobial treatment of infection was the most important independent determinant of hospital mortality for the entire patient cohort (adjusted OR, 4.27; 95% CI, 3.35 to 5.44; p<0.001). Observational studies suggest a significant reduction in mortality when antibiotics are administered within 4[22] and 8 hours[23] of hospital presentation (p<0.01). In our study we also were able

to demonstrate a statistically significant relationship between early administration of antibiotics and survival, the crude odds ratio of 0.70 (95% CI, 0.63 to 0.98, p=0.04) indicates a protective effect when antibiotics were given early.

Our study is unique since it is the first study from the Indian Subcontinent to address the issue of timely antibiotic administration in the ED setting. Our study population also differs from those in other trials by the overwhelming prevalence of blood stream sepsis with Salmonella typhi, which in itself had an unadjusted mortality rate of 18%. However our results are comparable to other studies, with similar rates of appropriate antibiotic administration (64% comparable to the 63%–84% reported in the literature[27–31]) and overall mortality.

In our study, aggressive intravenous fluid resuscitation was carried out in almost half the patients presenting with sepsis but less than that recommended by the guidelines.[7] The average timing of antibiotics delivered in septic shock patients was 2.3 hours. Kumar *et al*[32] recently published a recommendation to start broad spectrum antibiotics in septic shock patients within an hour of onset of hypotension. We are not alone in our non-adherence to guidelines. Literature from the West also suggests that adherence is improved by instituting protocols and order sets. Micek *et al*[33] recently reported that only after implementation of a standardised protocol did their ED resuscitative measurers approach those recommended by the Surviving Sepsis Guidelines.

Although our survival rates are well within international standards and our timing of initiation of antimicrobial therapy may be acceptable, 100% of our septic shock patients died. Though the numbers are too small to draw concrete conclusions, it would seem likely that the excess mortality may have been related to inappropriate choices of antibiotics and a lack of goal-directed fluid resuscitation.

One important limitation of our study is that only 67% patients received appropriate antibiotics in the emergency room. This underscores the importance of recognizing and documenting local microbiological patterns of pathogenicity and drug sensitivity.

CONCLUSIONS

Our data suggest that in the care of patients presenting with Sepsis to the Emergency Department, the longer the delay in receiving antibiotics, the more adverse the outcomes. Adhering to the early goal-directed therapy and antibiotic recommendations of the Surviving Sepsis guidelines may alter the inevitable downward spiral of severe sepsis and shock. Certainly prevention is the better part of the cure, and especially so for financially strapped developing countries unable to bear the burden of critical illness.

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