Early Antibiotic Therapy (EAT) Decreases In-Hospital Mortality of Patients with Sepsis at the Emergency Department

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Abstract

Introduction: Septic shock is the most common type of shock encountered by internists and is the most common cause of death in non-coronary intensive care units. In the 2012 Surviving Sepsis Campaign, one recommendation is antibiotic administration within three hours from sepsis recognition. Several large-scale studies challenged this recommendation with contrasting results. The researchers aim to determine the impact of early antibiotic therapy (EAT) on mortality and outcome of patients and to determine institutional compliance to current sepsis recommendations.

Methods: This retrospective single center study included septic patients at the emergency room from February 2013 to January 2015 and were grouped into the EAT group (lesser than or equal to three hours) and control group (more than three hours) antibiotic initiation from sepsis recognition). Primary outcomes are in-hospital mortality, time-to-antibiotics and extraction of blood culture prior to antibiotics. Secondary outcomes include length of hospital stay, use of vasopressors and mechanical ventilation and development of sepsis-related complications.

Results: Two-hundred sixty-one patients were included with 53.26% overall mortality rate. The overall mean time-to-antibiotics is 355.1 minutes and time-to-blood culture is 434.64 minutes. Mean time-to-antibiotics were 115 and 556 minutes in the EAT and control group respectively. Mortality was significantly higher in the control group (43.7% vs. 61.3%, p=0.006). For the sepsis related complications, development of acute kidney injury (p=0.033) was higher in the EAT group and acute respiratory failure (p=0.009) was significantly increased in the control group.

Conclusion: Antibiotic administration within three hours from sepsis recognition significantly reduced in-hospital mortality. Timing of antibiotics and collection of blood cultures were delayed compared to current recommendations. Among the sepsis-related complications, prolonged time-to-antibiotics (>3 hours) is associated with risk of developing acute respiratory failure and subsequent need for mechanical ventilation.

Keywords: early antibiotic therapy, septic shock, sepsis, systemic inflammatory response syndrome

Introduction

Severe sepsis and septic shock remain to be significant causes of morbidity and mortality in hospitalized patients worldwide. Both are worrisome manifestations of systemic infection and the leading causes of hospitalization in intensive care units (ICUs), where an estimated 19 million cases occur worldwide each year, resulting in the death of one in four of these patients.[1] Septic shock is the most common type of shock encountered by internists and sepsis has been reported as the most common cause of death in non-coronary intensive care units.[2]

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A recent study on the global burden of sepsis involving seven high-income countries showed the population incidence rate from 1979 to 2015 was 288 and 148 cases per 100,000 person-years for hospital-treated sepsis and hospital-treated severe sepsis cases respectively. In the last decade, the incidence rate was 437 and 270 per 100,000 person-years for sepsis and for severe sepsis respectively. Hospital mortality was 17% for sepsis and 26% for severe sepsis. There were no population-level sepsis incidence estimates from lower-income countries.[3] The sepsis syndromes are lethal and expensive conditions, with hospital mortality rates for severe sepsis ranging between 30% and 50%.[4]

There are only a few studies on sepsis in the Philippine setting. There is no published paper on the sepsis burden of illness nor data on overall sepsis prevalence in the country but data from individual hospitals exist. A local study on outcome of patients with bacteremia showed that the mortality rate was 37%. In terms of treatment, results show

that comparatively more survivors were given adequate (92% vs. 69%; *p*-value=0.0127) and undelayed (90% vs. 66%; *p*-value=0.0197) treatment than non-survivors.[5] Another local study on epidemiology and predictors of mortality from sepsis published in 2000 demonstrated 77% sepsis-related mortality, with septic shock (42%) and multi-organ failure (38%) as immediate causes of death. Prevalence of sepsis was 25% with an all-cause mortality of 34% in this population.[2] Another study on epidemiology and outcome of bacteremia showed that 94 out of the 135 patients with bacteremia survived (35% mortality rate).[6] A more recent study involved 1,207 patients screened, 223 patients (18.5 percent) had severe sepsis and mortality rate was 58.9%.[7]

Despite development of broader spectrum antibiotics and advances in intensive care through the years, sepsis-related mortality rates locally and abroad have been similar. Recommended research strategies are those targeted towards the modifiable factors associated with mortality to help reduce the unacceptably high mortality rate. These quality improvement strategies should focus on: 1) prompt initiation of appropriate antimicrobial therapy; 2) early recognition of organ dysfunction and initiation of goal-directed therapy; and 3) aggressive monitoring of immunocompromised patients for early signs of sepsis.[7]

In the Surviving Sepsis Campaign published last 2012, an early goal-directed therapy (EGDT) approach to the management of sepsis including septic shock was recommended. One goal of therapy is administration of effective intravenous antimicrobials within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C). Of note is a remark mentioning that although the weight of the evidence supports prompt administration of antibiotics following the recognition of severe sepsis and septic shock, the feasibility with which clinicians may achieve this ideal state has not been evaluated.[1] Several sepsis bundles to be accomplished within three hours were also emphasized and these include the following: 1) measurement lactate level, 2) collection of blood cultures prior to administration of antibiotics, 3) administration of broad spectrum antibiotics, 4) administration of 30 ml/kg crystalloid for hypotension or lactate 4mmol/l. Other bundles to be completed within six hours include: 1) initiation of vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) 65 mmhg; 2) in the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate 4 mmol/l (36 mg/dl), other procedures recommended are to measure central venous pressure (CVP) and central venous oxygen saturation; 3) remeasure lactate if initial lactate was elevated.[1]

Through the recent years, there have been contrasting results of studies on EGDT versus conventional approach to sepsis management. Several foreign multicenter trials conducted in the tertiary care setting challenged this recommended protocol-based management of patients in whom severe sepsis and septic shock was diagnosed in the emergency department. The ARISE study (n=1600), the ProCESS trial (n=1341) and the ProMISe trial (n=1260) all concluded that EGDT did not reduce mortality at 90-days.[8,9,10] In a recent meta-analysis including 10 randomized controlled trials (RCTs) from 2001 to 2014 involving 4,157 patients comparing EGDT to controls, EGDT was not associated with a survival benefit among patients with severe sepsis or septic shock.[11]

In contrast to above studies, a larger-scale retrospective analysis of a dataset from 165 ICUs in Europe, United States and South collected prospectively from January 2005 through February 2010 for the Surviving Sepsis Campaign was published last 2014. A total of 17,990 patients were included in the analysis. In-hospital mortality was 29.7% for the cohort as a whole. The study demonstrated a significant association between delay in antibiotic administration over the first six hours after identification of patients with severe sepsis and septic shock and increasing in-hospital mortality. In addition, there was a linear increase in the risk of mortality for each hour delay in antibiotic administration.[12] Moreover, another study by Ortega showed that implementation of the Surviving Sepsis Campaign guidelines was associated with a significant decrease in mortality.[13]

Several studies abroad also focused on association of timing of antibiotic initiation and patient outcomes. A prospective cohort study in Pennsylvania (n=261) found that in-hospital mortality was 31%. Median time from triage to antibiotics was 119 minutes. When mortality was analyzed for time from triage to appropriate antibiotics, there was significant association at the <1 hr (*p*=0.02) time cutoff; similarly, for time from qualification for EGDT to appropriate antibiotics, a significant association was seen at the <1 hr (*p*=0.03) time cutoff.[14] The INITIAT-E.D. trial in Australia (n=220) demonstrated that the median time to antibiotic administration was 3.5 hours and in-hospital mortality was 28.6%. There was no association observed between delays to antibiotics and mortality in the total patient population. When stratified by presenting severity, patients with severe sepsis demonstrated a trend towards increased mortality when delays to antibiotics exceeded six hours from triage in comparison with <1 hour.[15] These contrasting results from different international studies lead to the development of this current local study.

At the time of conceptualization of this paper, there is no locally published study comparing EAT and usual protocol of care in sepsis. Most of the internationally published data only focused on patients with severe sepsis and septic shock. This paper included all patients diagnosed with sepsis regardless of severity. There is also no local study determining compliance to specific bundles of care that are applicable in the local setting.

This study aims to determine the impact of EAT on outcome of patients with sepsis at the emergency department. The study also aims to determine institutional compliance to recommended timing of blood culture specimen and initiation of antibiotics. The specific objectives are: 1) to determine time-to-antibiotics and its impact to sepsis-related morbidity and mortality; 2) to determine the impact of EAT on length of hospital stay, use of vasopressor and mechanical ventilation and development of sepsis-related complications.

Methods

This is a single-center retrospective chart review of patients seen at the emergency department of a tertiary specialty hospital between February 2013 and January 2015. Patient records were searched using DocuView available at the medical records section and identified using International Classification of Diseases Revision 10 codes for sepsis and sepsis-related conditions (A40 and A41).

All patients >18 years old who fulfilled the American College of Chest Physicians/Society of Critical Care Medicine Consensus criteria on sepsis, SIRS and septic shock were included in the study population.[16]

Patients with severe sepsis were classified as those who fulfill the criteria for sepsis and have at least one of the following signs of hypoperfusion or organ dysfunction that is new and not explained by other known etiology of organ dysfunction: hypotension (MAP <65), areas of mottled skin or capillary refill >3 seconds, creatinine >2.0 mg/dL, disseminated intravascular coagulation (DIC), platelet count <100,000 cells/μL, acute renal failure or urine output <0.5 ml/kg/hr for at least two hours, hepatic dysfunction as evidence by bilirubin >2 or INR >1.5, cardiac dysfunction, acute lung injury or failure.

Patients are excluded if with the following: known pregnancy, drug overdose, injury from burn or trauma, haemodynamic instability due to active haemorrhage, had emergency/immediate surgery, known history of AIDS, do-not-Intubate (DNI) status, transferred from another in-hospital setting, discharged against medical advise (DAMA), patients with hospital-acquired infection, IV antibiotic use within the last 24 hours, did not receive antibiotics and those with primary diagnosis of an acute cerebral vascular event, seizure, acute coronary syndrome, acute pulmonary oedema, status asthmaticus, major cardiac arrhythmia (as part of primary diagnosis)

All patients who received antibiotics within 180 minutes (three hours) from the time of sepsis recognition were included under the EAT group and patients who received antibiotics for more than three hours were included in the control group.[1] Patient's demographic data, vital signs on admission, mean arterial pressure, sepsis severity, quick sequential sequential organ failure assessment (qSOFA) Score, comorbid conditions and source of infection were collected as part of baseline characteristics.

The qSOFA score is a new sepsis severity scoring system recommended by the Sepsis-3 Consensus. Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside using the following parameters 1) alteration in mental status, 2) systolic blood pressure ≤100mmHg, 3) respiratory rate ≥22/min. Each fulfilled parameter corresponds to a score of one.[17]

The primary outcomes are to determine mortality between patients who received antibiotics 180 minutes (three hours) from sepsis recognition. Other outcomes include institutional compliance to recommended bundles of care in the management of sepsis specifically to determine the overall time-to-antibiotics, time-to-blood CS and if blood CS was obtained prior to initiation of antibiotics.

Secondary outcomes include length of hospital stay, use of vasopressors, need for mechanical ventilation and development of sepsis-related complications including acute respiratory failure, acute kidney injury, septic encephalopathy, hepatic failure, disseminated intravascular coagulation.

Categorical data were represented as frequency and proportion. Analysis of categorical data was done using pearson chi-square and fisher's exact test. Continuous data were represented as mean ± standard deviation and were analyzed using independent sample t-test. All tests of significance are two-tailed and alpha was set at 0.05. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) v20.0.

This study was approved by the Research Ethics Committee (REC) of the National Kidney and Transplant Institute, Quezon City, Philippines. Study subjects were identified using numerical codes to maintain privacy. Only the primary investigator has the access to the pool of patient data included in this study.

Results

A total of 780 patients with sepsis at the emergency room were screened and 261 were included in the final analysis (Figure 1)

Table I summarizes the patient characteristics. Groups are comparable in terms of age distribution (p=0.052), gender (p=0.711), mean heart rate (p=0.055), mean respiratory rate (p=0.381), severity of illness (p=0.491) and qSOFA score (p=0.309). Mean arterial pressure was significantly lower (p=0.011) and mean temperature was significantly elevated (p=0.024) in the EAT group. The groups

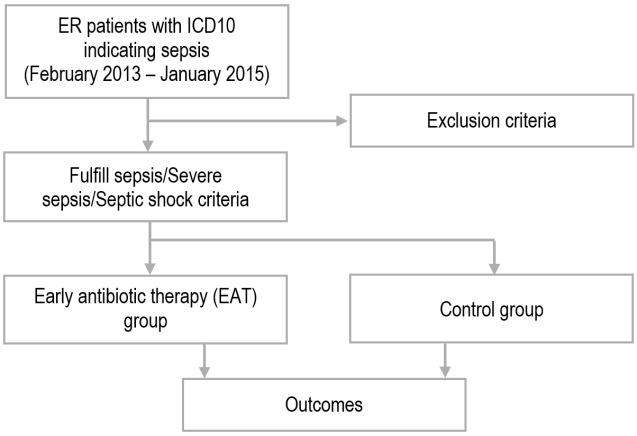

Figure 1. Flowchart of patients presenting to the emergency department with sepsis

Table I. Baseline characteristics of patients under EAT group versus control group

Patient characteristics	EAT group n=119	Control group n=142	*p*-value
Age (mean ± SD)	60.84 ± 19.03	56.50 ± 16.50	0.052
Gender [n,(%)]			
Male	60 (50.4%)	75 (52.8%)	0.711
Female	59 (49.6%)	67 (47.2%)	
Sepsis screening (mean ± SD)			
Mean arterial pressure (mm Hg)	77.96 ± 20.73	84.39 ± 19.89	0.011
Heart rate (beats/min)	97.84 ± 19.65	93.11 ± 19.80	0.055
Respiratory rate (breaths/min)	23.60 ± 4.62	23.16 ± 3.37	0.381
Temperature (°C)	37.75 ± 1.34	37.39 ± 1.18	0.024
Severity of illness [n,(%)]			
Sepsis	18 (15.1%)	23 (16.2%)	0.491
Severe sepsis	39 (32.8%)	37 (26.1%)	
Septic shock	62 (52.1%)	82 (57.7%)	
qSOFA score [n,(%)]			
0	11 (9.2%)	15 (10.6%)	0.309
1	49 (41.2%)	73 (51.4%)	
2	45 (37.8%)	42 (29.6%)	
3	14 (11.8%)	12 (8.5%)	
Comorbid conditions [n,(%)]			
Diabetes mellitus	45 (37.8%)	53 (37.3%)	1.000
Hypertension	57 (47.9%)	71 (50%)	0.804
Chronic kidney disease	43 (36.1%)	79 (55.6%)	0.002
HD	31 (26.1%)	45 (31.7%)	0.341
PD	3 (2.5%)	15 (10.6%)	0.009
Post kidney transplant	7 (5.9%)	6 (4.2%)	0.370
Malignancy	25 (21%)	7 (19%)	0.756
Source of infection [n,(%)]			
Urinary tract	30 (25.2%)	37 (26.1%)	0.888
Pneumonia	55 (46.2%)	65 (45.8%)	1.000
Abdomen	23 (19.3%)	31 (21.8%)	0.648
Soft tissue and skin	22 (18.5%)	27 (19%)	1.000
CRBSI*	13 (10.9%)	15 (10.6%)	1.000
Mixed (>one source)	31 (26.1%)	35 (24.6%)	0.886

**Catheter related blood stream infection*

are also similar in terms of comorbid conditions except for patients having chronic kidney disease (*p*=0.002) specifically those on peritoneal dialysis which is significantly higher in the control group (*p*=0.009). Both groups are comparable in terms of source of infection (all *p*-values >0.05).

The overall mortality is 139 of 261 patients (53.26%). The mean time-to-antibiotic is 355.1 minutes (5.92 hours) and the mean time for collection of blood CS is 434.64 (7.24 hours). Only 21 patients received antibiotics within the first hour of sepsis recognition and majority of patients have received antibiotics more than than three-hour recommended time period (54.4%). Mortality was significant higher among patients who received antibiotics for >180 minutes (EAT group=43.7%, control group 61.3%) (*p*=0.006). Blood culture was obtained only in 119 out of 261 patients with no significant difference when comparing in between groups. The average time-to-antibiotics in the EAT group was 115 minutes (1.92 hours) (Table II).

Table II. Comparison of primary outcomes between EAT group versus control group

Primary outcomes	Total n = 261	EAT group n = 119	Control group n = 142	*p*-value
In-hospital mortality(n)	139(53.26%)	52(43.7%)	87(61.3%)	0.006
In-hospital time to mortality (days)	6.87	5.81 ± 5.53	7.48 ± 5.81	0.096
Blood culture prior to antibiotics (n)	119(45.59%)	52(43.7%)	67(47.2%)	0.618
Time-to-blood CS (mins)	434.64	273.27±547.38	587.59±1096.11	0.014
Time to antibiotics (mins)	355.1	114.63 ±44.65	557 ± 625.16	<0.001
Timing of antibiotics				
<60 minutes	21 (8.05%)	21 (17.6%)	-	-
<180 minutes	119 (45.59%)	119 (100%)	-	
>180 minutes	142 (54.4%)	-	142 (100%)	
> 360 minutes	68 (26.05%)	-	68 (47.9%)	

Table III. Comparison of secondary outcomes between EAT group versus control group

Secondary outcomes	EAT group n = 119	Control group n = 142	*p*-value
Duration of hospital stay (days)	9.72 ± 8.64	9.93 ± 7.64	0.837
Vasopressor use (n)	60 (50.4%)	78 (54.9%)	0.534
Mechanical ventilation (n)	47 (39.5%)	79 (55.6%)	0.013
Complications (n)			
DIC	5 (4.2%)	7 (4.9%)	1.000
Hepatic failure	17 (14.3%)	11 (7.7%)	0.109
Septic encephalopathy	49 (41.2%)	67 (47.2%)	0.382
Acute respiratory failure	51 (42.9%)	84 (59.2%)	0.009
Acute kidney injury	39 (32.8%)	29 (20.4%)	0.033

Duration of hospital stay was similar between groups. Need for vasopressor therapy was also comparable. Use of mechanical ventilator support was also much higher in the control group (*p*=0.013). As for the sepsis related complications, more patients in the EAT group developed acute kidney injury (*p*=0.033). Acute respiratory failure (*p*=0.009) was more frequent among patients in the control group (Table III).

Discussion

In this single center study, the overall sepsis-related mortality of 53.2% is higher compared to an international large-scale multicenter study with 30% mortality rate.[12] However, when compared to previous locally published data, the result is similar with a mortality rate range of 30-70%.[5,6,7] Overall results in this study showed that there is a delay in antibiotic initiation with a mean duration of

approximately six hours compared to the recommended three-hour duration.[1] In the recommendations, blood culture specimen should be obtained prior to antibiotic initiation however this study demonstrated that the approximate time for blood culture extraction is even longer at 7.2 hours compared to antibiotic initiation. In a local study, delay in treatment was due to financial constraints in 33% of cases.[5] Even for differences between the groups, time for collection of blood CS is prolonged compared to initiation of antibiotics. It is also important to note that among the comorbidities, chronic kidney disease is higher in the control group.

In this study, the leading source in infection is the respiratory tract followed by urinary tract, intraabdominal, skin and soft tissue and CRBSI as foci of infection. The result is similar compared to a local paper by Alejandria et al. at the Philippine General Hospital (PGH) in 2000. Source of infection was predominantly community acquired pneumonia followed by skin and soft tissue, gastrointestinal and genitourinary.[7]

Proper approaches to sepsis management have been emphasized in the Surviving Sepsis Campaign including the different bundles of care to be accomplished within specific periods of time. Initiation of antibiotics within the first three hours has been recommended.[1] In reviewing the baseline demographic data, patients in the EAT group had significantly lower mean arterial pressures and increased temperatures but despite these factors that could have contributed to poorer outcomes, survival rate in the EAT group is significantly higher compared to patients in the control group. This relationship in the delay of antibiotics and mortality risk has been demonstrated by the very database from which the guideline was lifted. In the study by Ferrer et al., there was a linear increase in the risk of mortality associated with each hour of delay in antibiotic administration. This large-scale trial however included only patients diagnosed with severe sepsis and septic shock.[12] Although not statistically significant, majority of the patients included in this study are categorized under severe sepsis and septic shock. In terms of the qSOFA score, most scores are between qSOFA 1-2. In terms of development of sepsis-related complications, development of acute respiratory failure with subsequent need for intubation and mechanical ventilation is higher in the control group.

This study was conducted in a specialty tertiary hospital hence results may not be generalizable. Limitations of this study include assessment of time to recognition of sepsis, identification of microbiologic features and assessment of appropriateness of initial therapy. Studies on factors affecting delay of blood CS collection and antibiotic initiation may be done. Data collected in this paper could be a potential baseline database for a quality improvement study and creation of an institution-based protocol for sepsis management.

Conclusion

Early initiation of antibiotic therapy within three hours from recognition of sepsis demonstrated decreased risk for mortality. Timing of antibiotics and collection of blood cultures were delayed compared to current recommendations. No benefit was demonstrated on hospital stay and need for vasopressors. Among the complications associated with sepsis, prolonged time-to-antibiotics (more than three hours) is associated with risk of developing acute respiratory failure and subsequent need for mechanical ventilation.

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