Admission source predicts delay to antimicrobial therapy in septic shock - a retrospective cohort study

Jeremy Fernando, Takayoshi Ikeda, Alex Psirides, Paul Young

Abstract

***Objective*: To evaluate whether Intensive Care Unit (ICU) admission source predicts delay in the prescription of appropriate antimicrobial therapy in patients with septic shock.**

***Design, Setting and Participants*: Single-centre, retrospective cohort study at a tertiary ICU in Wellington, New Zealand. All adult patients admitted with septic shock between 2003 and 2010 were included in the study.**

***Main outcome measures*: Data including demographics, APACHE III score and diagnosis, source of admission, microbiological data, onset of hypotension, and the time to appropriate antimicrobial therapy (T_{AAT}) were collected from the Wellington ICU database and the medical records. Outcome data including the duration of mechanical ventilation, ICU and in-hospital mortality, hospital length of stay, and vital status at 6 months were collected.**

***Results*: 107 patients were identified. 93 had sufficient data to calculate T_{AAT} (median 16 minutes, interquartile range [IQR] 0-105). Cox modelling demonstrated no significant difference in T_{AAT} based on admission source (log rank test=0, df=2, p>0.5); however, when a sensitivity analysis was performed excluding 43 patients in whom antibiotics were administered prior to the onset of shock and one outlying patient with fungaemia, source of admission was found to be predictive of antimicrobial delay (log rank test=12.14, df=2, p<0.005). Among those patients who experienced any delay in antibiotic administration, the median T_{AAT} (IQR) for patients admitted from the ED, ward and regional hospitals was 58 (40-280), 180 (65-337), and 145 (120-544) minutes respectively.**

***Conclusions*: Our study suggests that ICU admission source is predictive of antimicrobial delay in patients with septic shock.**

Key words: Septic shock, source of admission.

Introduction

Sepsis is a common problem in critically ill patients and is associated with a high risk of death. (1-3) Specific therapies have been proven disappointing (4,5) and, with the possible exception of early goal directed therapy, an intervention tested in a small single centre RCT (6), treatment of septic shock is limited to provision of antimicrobials and supportive care. (7) Guidelines suggest that antimicrobials should be administered as a priority within 1 hour of the onset of septic shock. (7)

Patients with septic shock in the ward are different to patients in the Emergency Department (ED) as they are more likely to have nosocomial infections which are associated with higher mortality risk than community acquired infections. (8) Furthermore, the entire ED environment is designed to facilitate rapid diagnosis and treatment. One would expect

From Rockhampton Hospital, Rockhampton, Queensland, Australia (Jeremy Fernando), University of Otago, Wellington, New Zealand (Takayoshi Ikeda), Wellington Regional Hospital, Capital and Coast District Health Board, Wellington, New Zealand (Alex Psirides), and Medical Research Institute of New Zealand, Wellington, New Zealand (Paul Young).

Address for correspondence:

Dr. Jeremy Fernando

Intensive Care Unit, Rockhampton Hospital

Rockhampton, Queensland, Australia

Email: Jeremy_Fernando@health.qld.gov.au

that these factors would mean that patients admitted to the Intensive Care Unit (ICU) from the ED would be more likely to receive antibiotics in a timely fashion than those admitted from hospital wards. However, the extent to which ICU admission source impacts the time it takes until appropriate antibiotics are administered after onset of shock is unknown. With that in mind, we conducted a retrospective cohort study to establish whether or not ICU admission source was a predictor of antimicrobial delay in our institution.

Methods

Study design, participants, and setting

Single-centre, retrospective cohort study of patients ≥18 years of age admitted to Wellington ICU with an APACHE III diagnosis of septic shock between 2003 and 2010.

Wellington ICU is a tertiary ICU with approximately 1,500 admissions per year and provides intensive and high dependency care for a wide range of specialities including cardiothoracic surgery, neurosurgery, general and upper gastrointestinal surgery, ear, nose and throat and head and neck surgery, vascular surgery, and trauma as well as general medical and subspecialty patients. Wellington ICU also provides a 24 hour retrieval service for central New Zealand.

Ethics approval

Ethics approval for this low-risk observational study was provided by the New Zealand Multi-Region Ethics Committee (ethics reference number: MEC/11/EXP/072). The requirement for individual patient consent was waived.

Data extraction

A search of the Wellington Intensive Care database was carried out to identify all patients ≥18 years admitted to the ICU between 2003 and 2010 with an APACHE III diagnosis of 'sepsis with shock'. Data obtained from clinical records included source of admission, place of onset of hypotension, primary team looking after patient, source of sepsis, length of mechanical ventilation, length of stay in hospital and mortality (ICU, in hospital and 6 month post-ICU discharge). Six-month mortality was determined using data from the New Zealand National Death Registry.

All microbiological results for specimens taken within 48 hours from onset of hypotension were reviewed. A microbiological specimen was deemed pathogenic if a positive blood culture was found or a culture was positive from the symptomatic site. All coagulase negative Staphylococcus blood cultures were considered to be contaminants unless a review of the clinical record indicated they were regarded as likely to be pathogenic by treating clinicians. Organism culture and sensitivities were recorded and compared to the antimicrobials administered.

Patients' medical records were reviewed to identify: (1) the time of onset of hypotension defined by a systolic blood pressure of <90 mmHg or the commencement of noradrenaline (T0), (2) the time after onset of hypotension when a doctor reviewed the patient (T1), and, (3) the time at which appropriate antimicrobials were administered (T2). The T_{AAT} was defined as the amount of time between onset of shock and administration of appropriate antibiotics. If hypotension was documented in the ambulance en route to the hospital, T0 was defined as the ED triage time. The time that the patient was first reviewed by a doctor was defined as the time recorded in the medical or nursing notes. When this information was not recorded, the time was inferred from the time when an arterial blood gas was performed on the basis that arterial blood gases are taken by doctors in our institution.

Appropriate antimicrobial therapy was defined as either the cultured organism being sensitive to the given antimicrobial or, if no organism was cultured, then as empiric therapy given in keeping with the local antimicrobial guidelines at the time of ICU admission. (9-11) If the initial antimicrobial administered was proven to be inappropriate on the basis of culture results, the time until administration of appropriate antimicrobials was used to define T2. All negative time delays (patients receiving appropriate antimicrobial therapy prior to onset of hypotension) were defined as zero (no delay).

Statistical analyses

All statistical analyses were conducted in R 2.13.2. (12) Continuous variables are presented as mean±standard

deviation (SD) and median±interquartile range [IQR] for parametric and non-parametric data, respectively. Categorical variables are reported as counts and percentages. Patients who did not have a time recorded when they received appropriate antimicrobials were removed prior to analysis as calculating the T_{AAT} was not possible. To analyse the T_{AAT} a Cox proportional hazards model was used. Cumulative events (Kaplan-Meier) curves were constructed to illustrate how probability of receiving appropriate antimicrobials changed with time between the differing sources of admission. Chi-squared tests were used to analyse whether there was a significant difference between sources of admission. Spearman's rank correlation tests were calculated to compare the T_{AAT} to the outcome variables. To assess the T_{AAT} with regard to mortality, t-tests were performed. The statistical significance level was set to p=0.05.

Results

From 2003 until 2010 inclusive there were 107 adult patients admitted to the ICU with APACHE III diagnosis of septic shock (**Table 1**). 93 patients had complete data to analyse the T_{AAT} (**Figure 1**). There were 62 men (58%) and the median age of all patients was 59 years (IQR 52-71). The median APACHE III score was 83 (IQR 66-95). Respiratory sepsis was the most common source of sepsis (31%). Twenty two percent of patients were culture negative. Nine patients experienced polymicrobial infection. The overall ICU mortality was 20.6% (95% CI 13.6-29.7). In-hospital mortality was 27.1% (95% CI 19.2-36.7), and six-month mortality was 38.3% (95% CI 29.2-48.3). **Figure 2** illustrates the proportions of time delays to appropriate antimicrobials. In the cohort 63% of patients received appropriate antimicrobials within 1 hour of hypotension onset.

There was no significant difference between the groups in terms of to the time until appropriate antimicrobial therapy was administered (**Figure 3**). 43 of 93 patients received antimicrobials prior to hypotension onset leaving 50 patients who experienced any delay in administration of antimicrobials after shock onset. When analysing the subgroup of patients who experienced any delay in antimicrobial therapy by source of admission there was still no difference between the groups (log rank test=5.31, df=2, p>0.05). However, one patient with candidaemia had a very long T_{AAT} of 4620 minutes. We performed a sensitivity analysis with the exclusion of this outlying patient. The results of the sensitivity analysis showed a significant difference in T_{AAT} between admission sources (log rank test=12.14, df=2, p<0.005). When the outlying patient and patients with no delay were excluded, the median T_{AAT} (IQR) for patients admitted from the ED, ward, and regional hospitals was 58 (40-280), 180 (65-337), and 145 (120-554) minutes respectively. Patients admitted from ED were more likely to receive appropriate antimicrobial therapy in a timely manner (**Figure 4**).

In our cohort, T_{AAT} had no significant correlation with APACHE III risk of death, length of mechanical ventilation (hours), ICU length of stay of survivors (days), or hospital length of stay of survivors (days).

Discussion

Our study suggests that ICU admission source is a predictor of delay to appropriate antimicrobial therapy. Patients admitted to the ICU from the ED appear more likely to receive appropriate antimicrobials in a timely manner. As far as we are aware, this is the first study to demonstrate that ICU source of admission is an important predictor of delays in appropriate administration of antimicrobial therapy.

Although our study was too small to show differences in outcome attributable to delays in antibiotic administration, existing retrospective studies suggest that delays in appropriate antibiotic administration are associated with adverse outcomes. A single centre cohort study of Emergency Department patients with severe sepsis or septic shock analysed the time to antibiotics in those that qualified for early goal directed therapy. (13) This study showed that there was a significant lower mortality in those patients who received appropriate antibiotics within 1 hour of qualifying for early goal directed therapy. Another retrospective study showed that for every hour a patient with septic shock is hypotensive and does not receive appropriate antimicrobial therapy is associated with an increase of mortality risk of 7.6%. (14) There is also evidence suggesting that early administration of appropriate antibiotics in patients with community-acquired pneumonia decreases mortality and hospital length of stay. (15)

Although the above retrospective studies have shaped our thinking about the timely administration of antimicrobials in septic shock and have formed the basis of the Surviving Sepsis Guidelines there are emerging data that challenge this paradigm. A recent pre-planned analysis of a randomized control trial of early sepsis resuscitation showed no increase in mortality for every hour delay in antimicrobial administration from triage; although, there was a mortality benefit for early antimicrobial therapy in patients who went on to develop shock. (16) Also, in community acquired pneumonia there have been subsequent studies that call into question the importance of early administration of antimicrobials. (17,18) For this reason, time to administration of antimicrobials in community acquired pneumonia has been removed as a measure of quality. (19)

Strengths and limitations of the study

Our study had several strengths, including a substantial time frame and the use of standardised predetermined definitions for determining of the T_{AAT}. Also, specific microbiological data were collected and then correlated with sensitivities and the local antimicrobial guidelines at the time of admission to intensive care.

We did not analyse whether or not there was a significant delay between charting of antimicrobials and administration of antimicrobials as many doctors used the term 'stat' rather than a specified time when charting urgent antimicrobials which means these delays cannot be determined retrospectively. Observer bias was minimized by having predefined definitions of the times of onset of hypotension, doctor review, and antimicrobial administration.

A limitation of our study is that it was a retrospective analysis. Another is that onset of hypotension was used to define shock onset rather using the accepted definition of septic shock which requires the presence of ongoing hypotension and organ dysfunction in the context of adequate fluid resuscitation. (7) Also, inclusion in the study was reliant on the APACHE III diagnosis being correct. There would have been many patients who were not included in the study despite having the clinical diagnosis of septic shock but having been given a disease specific APACHE III diagnosis rather than the general APACHE III diagnosis of septic shock. This would have led to an underestimation of the number of patients. Another limitation is that there was the significant difference in T_{AAT} only became apparent after the exclusion of a patient with candidaemia. A final limitation was that our study was underpowered to find a significant association between antimicrobial delays and patient centred outcome variables.

Summary and conclusions

Our study showed that admission source is a predictor of delay to appropriate antibiotic therapy in patients subsequently admitted to the ICU with septic shock. However, we were unable to demonstrate that this delay was associated with an increased risk of morbidity or mortality.

Table 1. Demographics and microbiology

	Admission Source		
	ED (n=39)	Ward (n=39)	Other hospital (n=29)
Age (median, IQR)	56 (42-71)	63 (59-69)	65 (54-73)
Gender (% male)	54	54	66
Ethnicity (n, %)			
NZE	24 (62)	25 (64)	22 (76)
Maori	5 (13)	3 (8)	3 (10)
Polynesian	3 (8)	5 (13)	2 (7)
Other	7 (18)	6 (15)	2 (7)
Source of infection (n)			
Abdomen	4	11	1
Blood	6	4	3
Cardiac	2	-	2
CNS	-	-	2
Musculoskeletal	3	2	6
Respiratory	13	11	9
Skin	2	1	-
Urological	6	5	5
Unknown	3	5	1
Organisms (n)			
Gram negatives			
Escherichia coli	5	7	5
Neisseria meningitidis	3	-	3
Proteus mirabilis	2	-	2
Pseudomonas species	2	3	1
Haemophilus influenzae	1	-	1
Citrobacter koseri	2	-	-
Klebsiella pneumoniae	-	1	-
Klebsiella pneumoniae (ESBL)	-	1	-
Serratia marcescens	-	1	-
Legionella	-	-	1
Burkholderia cepacia	-	-	1
Bacteroides thetaiotaomicron	-	1	-
Gram positives			
Staphylococcus aureus (MSSA)	9	4	10
Staphylococcus aureus (MRSA)	-	1	-
Streptococcus pyogenes	4	3	-
Enterococcus species	-	4	-
Streptococcus pneumoniae	1	1	1
Coagulase negative Staphylococci	2	-	-
Clostridium species	-	2	-
Listeria monocytogenes	-	-	1
Streptococcus salivarius	1	-	-
Peptostreptococcus	1	-	-
Streptococcus dysgalactiae	1	-	-
Streptococcus (Group G)	1	-	-
Alpha haemolytic Streptococcus	-	1	-
Fungi/yeasts			
Candida albicans	1	2	1
Unknown	6	13	5

Figure 1. Flow diagram illustrating patient categories

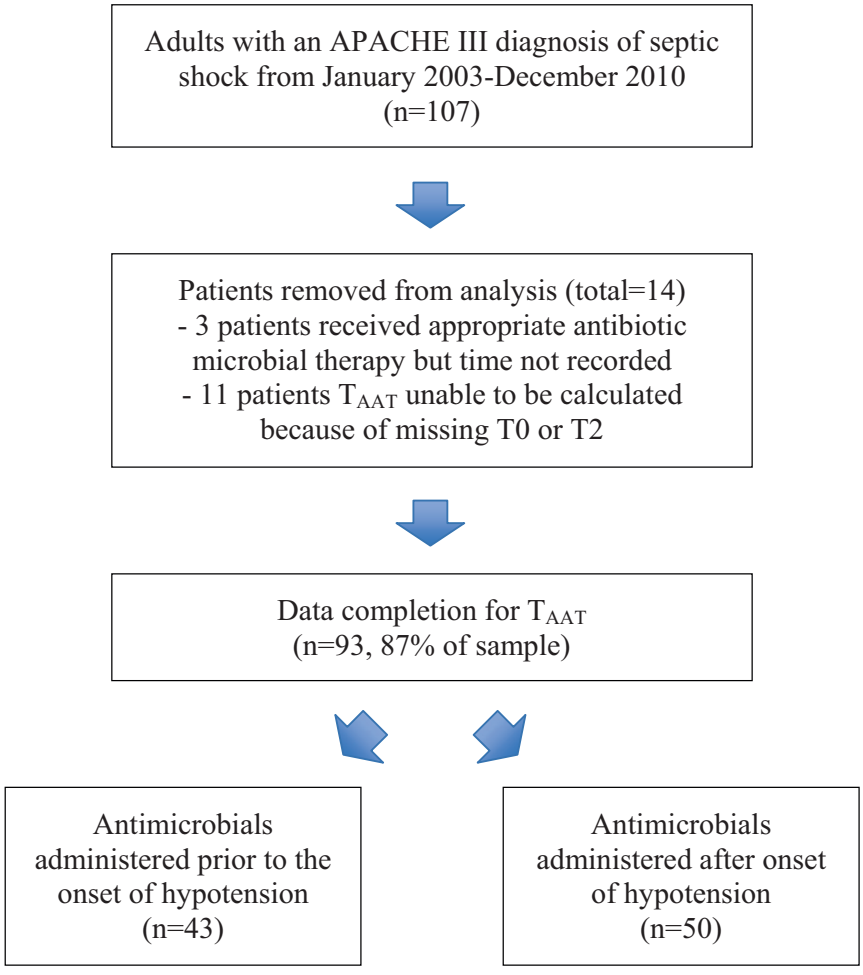


Figure 2. Proportions of time delays to appropriate antimicrobials

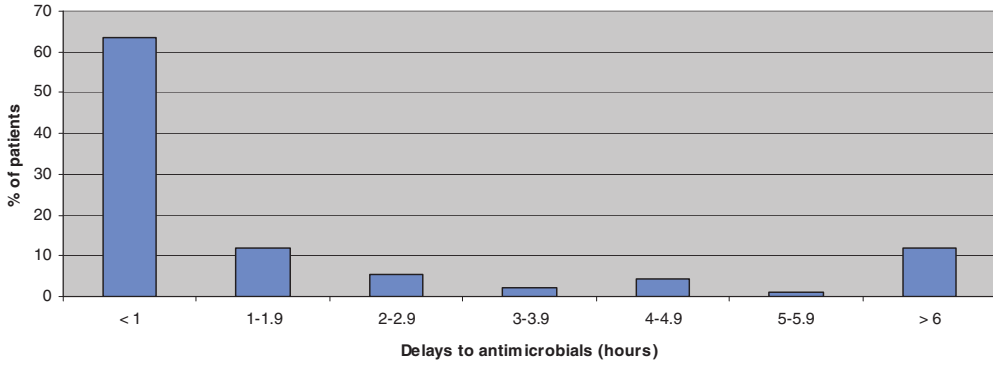


Figure 3. Whole cohort (n=93) - probability of receiving appropriate antimicrobials vs time from onset of hypotension

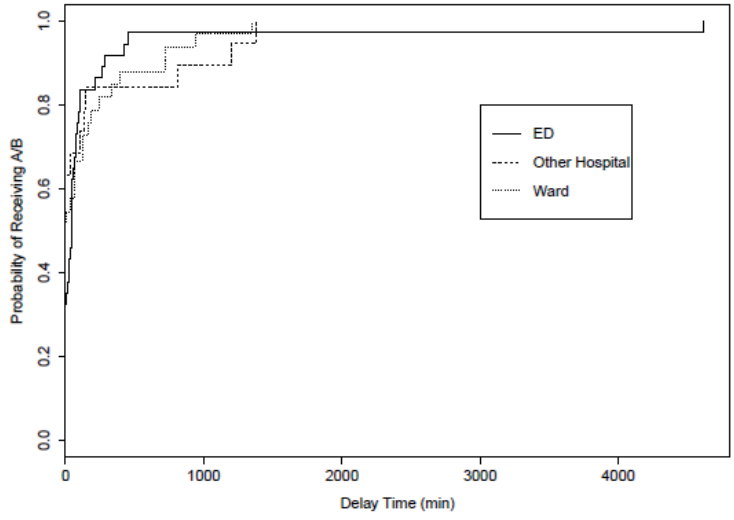
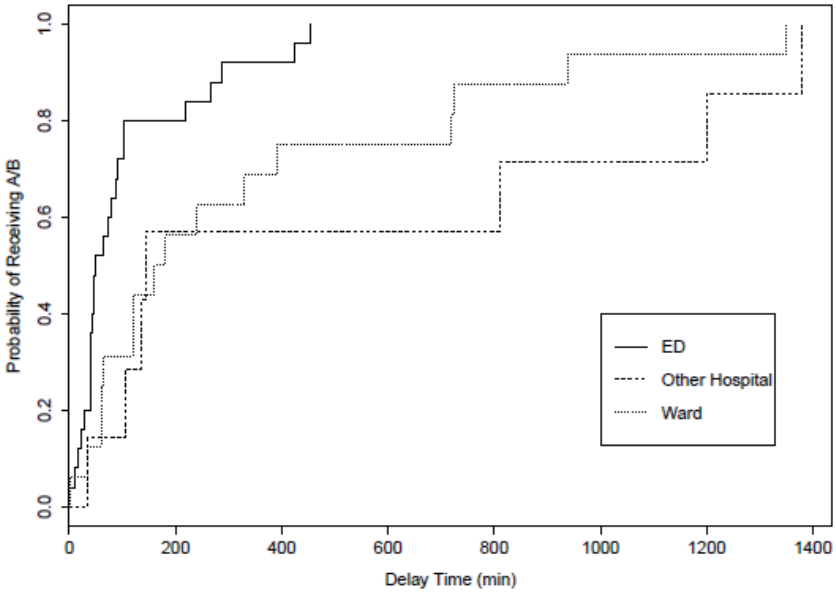


Figure 4. Analysis of those who experienced a delay to antimicrobial therapy from the onset of hypotension with exclusion of outlier (n=49) - probability of receiving appropriate antimicrobials vs time from onset of hypotension



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