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Indigenous Patients with Community Acquired Septic Shock Receive the Same Standard of Care as Non-Indigenous Patients in the Top End of Northern Territory, Australia

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Abstract

Introduction: Indigenous people have a fourfold higher incidence of sepsis in the Top End of the Northern Territory, Australia. However, their mortality from sepsis is not higher, despite an overall lower life expectancy, poorer access to healthcare, remoteness, higher chronic disease burden and social disadvantage. This suggests that Indigenous patients with sepsis receive the same standard of care as non-Indigenous patients; however, this has not been confirmed by investigation. The objective of the present study was to compare the early management of community acquired septic shock between Indigenous and Non-indigenous patients at the Royal Darwin Hospital (RDH) in the Top End of the Northern Territory, Australia.

Methods: Retrospective case note review of adult patients with septic shock admitted via the Emergency department (ED) of RDH between 01/01/2004 to 01/08/2005. Comparisons between Indigenous and Non-indigenous patients with septic shock were made with respect to: time to antibiotic, fluid resuscitation, time spent in the ED, mechanical ventilation, vasopressor use, continuous renal replacement therapy (CRRT), source control, Intensive Care Unit (ICU) length of stay (LOS), hospital LOS, and mortality.

Results: One hundred and twenty patients were included (69 Indigenous). Indigenous patients were younger, 46 (14) vs 54 (17) ($p=0.004$), with a higher chronic disease burden and similar Acute Physiology and Chronic Health Evaluation (APACHE) II scores, 20.1 (7.9) vs 20.7 (7.8). Indigenous patients had significantly higher rates of aeromedical retrieval, lower rates of self presentation ($p<0.05$), and a trend to more hypotension on arrival ($p=0.08$); suggesting that they had a delayed presentation compared with Non-indigenous patients. There were no significant differences in time to antibiotic, fluid resuscitation, time spent in the ED, mechanical ventilation, need for vasopressors, CRRT, source control, ICULOS, hospital LOS, and mortality. Another important finding was the positive culture rate from blood cultures taken after antibiotic administration was not significantly lower than the positive rate for blood cultures taken prior to antibiotic.

Conclusions: Management of community acquired septic shock in the Top End of Australia does not appear to differ between Indigenous and Non-indigenous patients; including compliance with surviving sepsis guidelines, antibiotic therapy, intensive care therapies and source control. While this is encouraging, the contributing factors leading to a higher burden of sepsis and septic shock in Indigenous people in the Top End needs further investigation. The study's findings also support the taking of blood cultures in septic shock, even if antibiotics have already been administered.

Keywords: Indigenous Patients; Septic Shock; Non-Indigenous Patients; Northern Territory; Australia

found that Indigenous patients had a fourfold higher incidence in hospital admissions for sepsis at the Royal Darwin Hospital (RDH) over a 12 month period [1]. At RDH, septic shock accounts for 24% of intensive care unit (ICU) admissions for Indigenous patients and 15% for Non-indigenous patients [2]. The overall mortality for sepsis requiring ICU admission in the Top End of Australia is comparatively low (25%), even by Australasian standards [1,3]. Importantly, the mortality from sepsis is not higher in Indigenous people, despite a lower life expectancy, poorer access to healthcare, higher chronic disease burden and social disadvantage [1]. One possible explanation is that Indigenous patients receive the same standard of treatment for septic shock as Non-indigenous patients, despite the coexistent health inequalities.

Timely recognition and management of community acquired septic shock in the Emergency Department (ED) is essential to minimize mortality. The Surviving Sepsis Campaign recommends a set of standardized evidence-based interventions within the first six hours of severe sepsis and septic shock, the so called resuscitation 'bundle' [4]. The recommendations include volume resuscitation, obtaining blood cultures prior to urgent administration of broad-spectrum antibiotics (within three hours), vasopressor support and early goal directed therapy (EGDT) [5]. As some components of these guidelines do not reflect Australasian practice, particularly EGDT, the Australian and New Zealand Intensive Care Society (ANZICS) decided not to sponsor the 2008 Surviving Sepsis Campaign in its entirety [6]. Despite this, mortality from septic shock in Australasia is lower than reported internationally (36% [7] versus up to 60% [8-10]).

The present study compared the early treatment of septic shock in Indigenous and Non-indigenous patients presenting to the ED at RDH to investigate why Indigenous patients have comparable septic shock outcomes despite significant health inequalities.

Methods

A retrospective case note review of adult patients with septic shock admitted via the ED of the RDH between 01/01/2004 to 01/08/2005 was performed. Demographic and treatment data were extracted from the case notes by two investigators. These two investigators reviewed a sample of charts prior to data collection to determine a uniform method for handling ambiguous or conflicting data.

Setting

The 339 bed RDH is the only tertiary referral teaching hospital in Darwin, the largest city in the tropical Top End of Australia with 56,000 presentations annually to the ED. Indigenous Australians account for 28% of ED presentations and 48% of ICU admissions.

Introduction

The Top End of the Northern Territory has Australia's highest incidence of sepsis, which is largely accounted for by the high burden of sepsis in its Indigenous population [1]. A large prospective study

Patient Enrollment

All adult (≥ 18 years) ED admissions with one or more of the International Classification of Diseases revision 10 (ICD-10) sepsis diagnostic codes (urinary sepsis with shock, non-urinary sepsis with shock, urinary sepsis, sepsis other than urinary and bacterial pneumonia) were identified from the RDH patient database. The case notes (including ambulance and aeromedical retrieval records) of these potentially eligible patients were assessed for the presence of septic shock; defined as two of four systemic inflammatory response syndrome criteria and a systolic blood pressure no more than 90mmHg (or a fall of more than 40mmHg from baseline) despite a crystalloid fluid challenge of at least 2 litres [11]. Only those with community-acquired septic shock were included; defined as shock onset at any time from pre hospital transport to within 24 hours of ED presentation. Readmissions (within 48 hours of discharge) and inter-hospital transfers of inpatients were excluded to prevent the inclusion of health care associated septic shock. Deaths occurring in the ED were excluded.

Microbiology results were collected for specimens taken within the period from 24 hours before to 48 hours after the onset of septic shock. Infections were considered to be proven if there was an isolated pathogen(s) appropriate to the clinical picture and/or by radiologic, surgical or pathologic diagnosis.

Indigenous vs Non-indigenous

Comparisons between Indigenous and Non-indigenous patients were made with respect to demographics, site of infection, septic shock treatment in the ED and ICU, time spent in the ED, APACHE (Acute Physiology and Chronic Health Evaluation) II scores, ICU and hospital length of stay (LOS), ICU and hospital mortality.

Treatment of Septic Shock

Compliance with the following components of the Surviving Sepsis Guidelines resuscitation bundle [4] was recorded;

- Collection of blood cultures prior to antibiotic administration.
- Administration of antibiotics within 3 hours of hypotension.
- Volume of fluid resuscitation.
- Vasopressor usage for hypotension not responding to fluid resuscitation of at least 2 litres.

EGDT was not practiced in the RDH ED during the study period and thus was not examined or reported. Intensive care therapies, in addition to the resuscitation bundle, were recorded and included the following; mechanical ventilation, continuous renal replacement therapy (CRRT); activated protein C; replacement dose corticosteroids; and granulocyte colony stimulating factor (G-CSF) or placebo as used in the coinciding RDH trial [6].

Ethics approval

The Human Research Ethics Committee of the Menzies School of Health Research and the NT Department of Health and Families approved the study and granted a waiver for informed consent (approval number 07/12)

Statistical Analysis

Data were entered into a Microsoft Excel 2007 spreadsheet. Statistical analysis was performed by SPSS (version15). Student's *t* tests were performed for continuous data. Fisher's exact tests were performed for categorical data. Data was expressed as mean (SD) unless otherwise stated. A *p* value of < 0.05 was considered significant.

Results

Patients

One hundred and twenty patients (58% Indigenous) were included in the study as outlined in Figure 1. Indigenous patients with septic shock were over-represented when compared to the 2006 NT census data (58% vs 28%) [12]. Demographic variables are presented in Table 1. The following demographic variables differed significantly according to indigenous status: age, gender, mode of presentation and some co-morbidities (Table 1). There was no difference in APACHE II score or ED disposition (Table 1). A higher proportion of Indigenous patients were hypotensive on arrival, but this was not statistically significant ($p = 0.08$).

Treatment of Septic Shock

Indigenous patients did not differ significantly with respect to compliance with the Surviving Sepsis resuscitation bundle, ICU management and source control (Table 2).

There were no differences in timing of antibiotic administration and blood culture sampling. The mean time to antibiotic administration was 8.2 hrs. Seventy two patients received antibiotics after the onset of hypotension, with only 44% receiving them within 3 hours (Table 2 and Figure 2). Blood cultures were collected in 117/120 (98%) of patients, 70/117 (60%) of which were taken prior to antibiotics (Figure 3).

Aetiology of Septic Shock

A focus of infection was identified in 94% of patients with lung being the most common site (Table 3). Forty percent of all blood

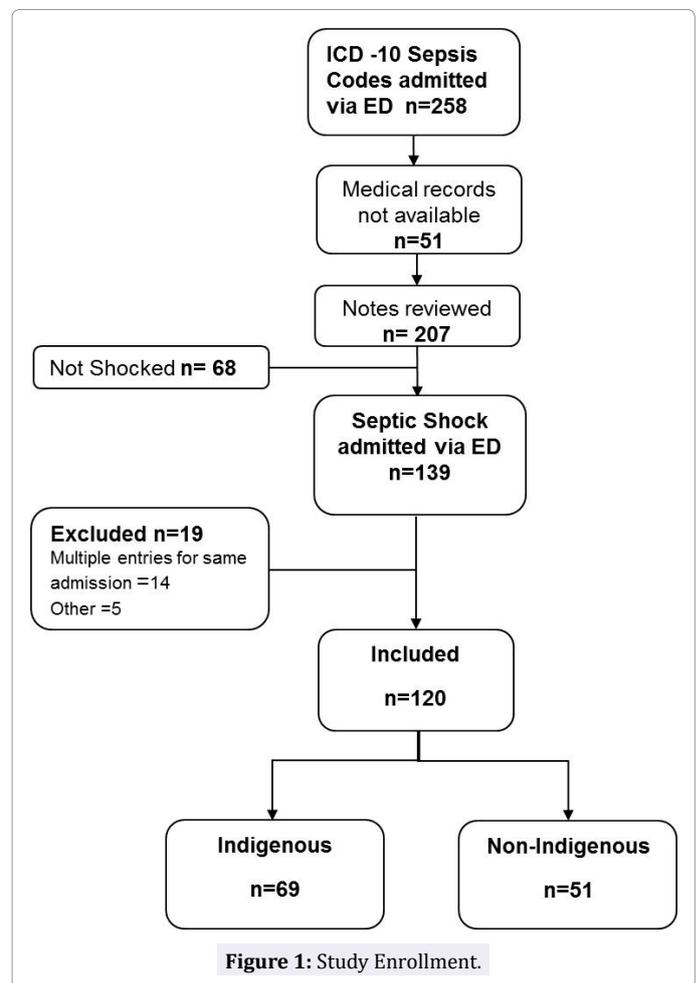


Figure 1: Study Enrollment.

Variable	All patients n = 120	Indigenous n = 69 (58%)	Non-indigenous n = 51 (43%)	P Value
Age; mean (SD) [†]	49.0 (15.8)	45.7 (13.9)	53.9 (17.1)	0.004
Male Gender; (%)	48%	36%	62%	0.006
Presented in wet season; (%)	40%	44%	35%	NS [‡]
Mode of presentation to Emergency Department; (%)				
Aeromedical retrieval	24%	38%	6%	< 0.001
Ambulance	52%	52%	51%	NS
Self Presentation	24%	10%	43	< 0.001
Hypotensive on arrival (%)	24%	30%	16%	NS
Time in Emergency Department prior to Intensive care Unit Admission:				
Number of hours; Mean (SD)	7.7 (5.0)	7.7 (5.0)	7.9 (4.9)	NS
< 4 hours; (%)	26%	28%	24%	NS
Emergency Department disposition: n (%)				
Intensive Care Unit	94 (78%)	57 (83%)	37 (73%)	NS
Ward	20 (17%)	9 (13%)	11 (22%)	NS
Operating Theatre	6 (5%)	3 (4%)	3 (6%)	NS
APACHE II score [§] ; mean (SD)	20.4 (7.8)	20.1 (7.9)	20.7 (7.8)	NS
Co-morbidities; n (%):				
Neutropenia	4 (3%)	1 (1%)	3(6%)	NS
Immunosuppression	6 (5%)	1 (1%)	5 (10%)	NS
Neoplastic disease	8 (7%)	3 (4%)	5 (10%)	NS
Liver Failure	15 (13%)	12 (17%)	3 (6%)	NS
Ischaemic heart disease	20 (17%)	11 (16%)	9 (18%)	NS
Congestive cardiac failure	7 (6%)	1 (1%)	6 (12%)	0.04
Chronic obstructive pulmonary disease	25 (21%)	19 (27%)	6 (12%)	0.04
End stage renal failure on dialysis	10 (8%)	9 (13%)	1 (2%)	0.04
Diabetes mellitus	40 (33%)	29 (42%)	11 (22%)	0.02
Hazardous alcohol use	42 (35%)	33 (48%)	9 (18%)	0.001

Table 1: Comparison of Indigenous vs. non-Indigenous patient characteristics, mode of hospital presentation, disease severity, emergency department duration and disposition

† SD = Standard deviation

‡NS = not significant; $p \geq 0.05$

§APACHE II score: Acute Physiology and Chronic Health Evaluation.

Variable	All Patients n = 120	Indigenous n = 69	Non-Indigenous n = 51	P-Value
Fluid Resuscitation in milliliters; mean(SD) [†]				
First 2 hours	1262 (1099)	1317 (1151)	1188 (1033)	NS [‡]
First 6 hours	2422 (1664)	2430 (1785)	2412 (1502)	NS
Time to antibiotic in relation to hypotension onset; n (%):				
Prior to onset of hypotension	47 (39%)	23 (33%)	24 (48%)	NS
After onset of hypotension	72 (61%)	46 (67%)	26 (51%)	NS
Time delay to antibiotic when given post hypotension :				
Number of hours: mean (SD)	8.2 (11.5)	8.5 (12.5)	7.2 (9.5)	NS
Given < 1hour; n (%)	18(25%)	12(26%)	6 (23%)	NS
Given < 3hours; n (%)	32 (44%)	22 (48%)	10 (39%)	NS
Given < 6hours; n (%)	43 (60%)	25 (54%)	18 (69%)	NS
Intensive care unit therapies: n [§] (%):				
Vasopressors	87 (74%)	50 (74%)	37 (74%)	NS
Mechanical ventilation	42 (36%)	27 (40%)	15 (30%)	NS
Continuous renal replacement therapy	31(26%)	16(24%)	15 (30%)	NS
Adjuvant therapies:				
Activated protein C				
Replacement dose Cortico steroids	3 (3%)	1 (1%)	2 (4%)	NS
Open label G-Colony Stimulating Factor	45 (38%)	29 (43%)	16 (32%)	NS
G-Colony Stimulating Factor(Study drug [‡])	5 (4%)	3 (4%)	2 (4%)	NS
	38 (32%)	21 (31%)	14 (33%)	NS
Source control; n (%):				
Operative	21 (18%)	12 (17%)	9 (18%)	NS
Non-Operative	2 (2%)	1 (1%)	1 (2%)	NS

Table 2: Comparison of septic shock treatment received in the Emergency Department and Intensive Care Unit for Indigenous vs. non-Indigenous patients.

† SD = Standard deviation

‡NS = not significant; $p \geq 0.05$

§ n = 117; total number of patients admitted to ICU

‡enrolled in Granulocyte colony stimulating factor in septic shock study [10]

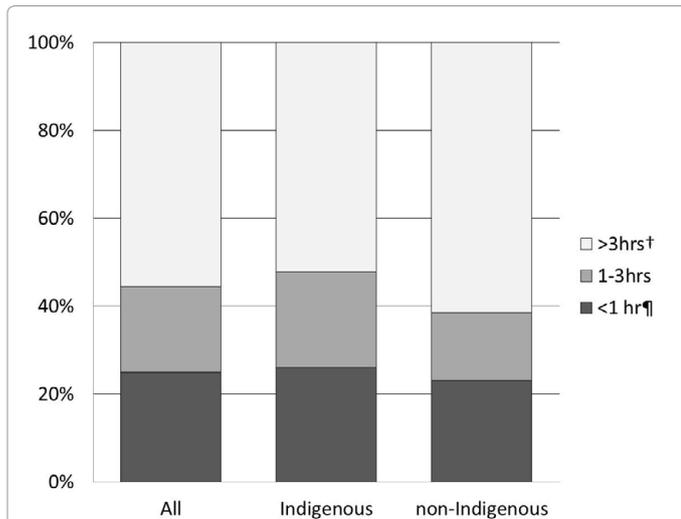


Figure 2: Time to antibiotic administration post hypotension in patients who received antibiotics after the onset of hypotension (n=72[§]).
 †P=0.7896; Fisher’s exact test; < 3hrs vs. > 3hrs, Indigenous vs. non-Indigenous.
 ¶P=1.00; Fisher’s exact test; < 1hr vs. > 1hr, Indigenous vs. non-Indigenous.
 §72/120 (61%) of patients had antibiotics after the onset of hypotension; 47/120 (39%) of patients had antibiotics prior to onset of hypotension, one patient had unknown time of antibiotic administration.

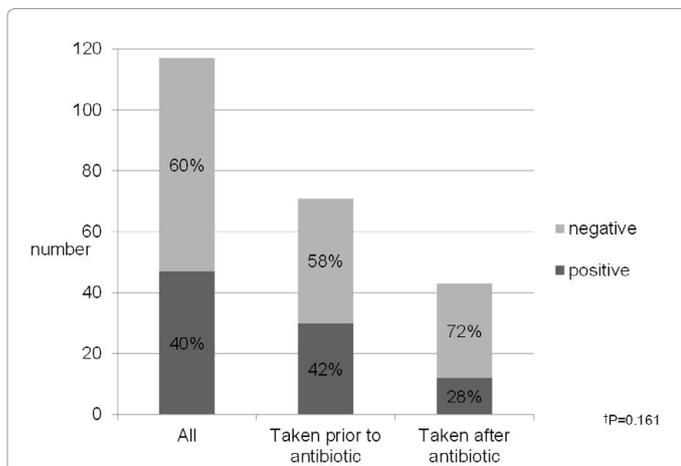


Figure 3: Blood culture results as a percentage of total (n=117) and comparison between samples taken prior to and after appropriate intravenous antibiotic administration.
 60% (70/117) had blood cultures taken prior to and 40% (47/117) after antibiotic administration.
 † Fisher’s exact test comparing positive cultures taken prior to and after blood culture.

cultures were positive. The administration of antibiotics prior to blood culture sampling did not significantly affect the percentage of blood cultures yielding a positive result (Figure 3). Site of infection did not differ between Indigenous and Non-indigenous patients. Organisms identified from any of the microbiological investigations are displayed in Table 4.

ICU Admission

Of the 120 patients included, 117 (67 Indigenous) were admitted to ICU within 24 hours of ED presentation, 94 directly (80%) and 23 (20%) via the ward or operating theatre (Table 1).

Site of Infection (%)	All patients n = 120	Indigenous n = 69	Non-indigenous n = 51	P Value
Lung	60%	65%	53%	NS†
Genitourinary	19%	15%	26%	NS
Skin and soft tissue	17%	15%	20%	NS
Intra-abdominal	7%	6%	8%	NS
Bone/Joint	3%	2%	4%	NS
Endocarditis	3%	3%	2%	NS
CNS	0%	0%	0%	NS
Other	4%	2%	8%	NS
Unknown	6%	4%	8%	NS
Multifocal	16%	12%	22%	NS

Table 3: Comparison of the sites of infection implicated as the source of septic shock, between Indigenous and non-Indigenous patients.
 † NS = not significant; p ≥ 0.05

Organisms†	N (%)
Gram Negative	48 (46)
Coliforms¶	26 (25)
Burkholderia pseudomallei	7 (7)
Acinetobacter spp.	5 (5)
Pseudomonas aeruginosa	5 (5)
Haemophilus influenza	5 (5)
Gram positive	49 (47)
Methicillin Sensitive Staphylococcus Aureus	19 (18)
Coagulase negative Staphylococci	5 (5)
MORSA/NORSA§	3 (3)
Streptococcus pneumonia	9 (9)
Streptococcus pyogenes	8 (8)
Other Streptococci	5 (5)
Anaerobes	6 (6)
Fungi- Penicillum marneffeii‡	1 (1)
Mycobacterium tuberculosis	1 (1)
Total Pathogens identified	105

Table 4: Primary microbiological pathogen implicated as the culprit organism for the episode of septic shock.
 †isolated from any microbiological investigation and not a contaminant, includes multiple organisms for some patients.
 ¶*Escherichia coli, Klebsiella, Proteus, Citrobacter, Enterobacter*
 §Multiresistant Oxacillin Resistant *Staphylococcus aureus*, Non-multiresistant Oxacillin Resistant *Staphylococcus aureus*
 ‡HIV infected individual.

Time in ED prior to ICU admission

Patients directly admitted to the ICU from the ED spent a mean of 7.7 hours (with 26% less than 4 hours); with no difference between Indigenous and Non-indigenous patients (Table 1).

ICU LOS, hospital LOS and Mortality

There were no significant differences in ICU LOS, 2.8 [1.8-5.9] vs 4.1 [2.4-7.3] (median [IQR]); hospital LOS, 10.9 [4.9-18.4] vs. 10.0 [6.0-19.9]; ICU mortality, 7/67 (10%) vs. 3/50 (6%); and hospital mortality, 16% vs. 10%, between Indigenous and Non-indigenous patients respectively. Overall ICU and hospital mortality was 8.5% and 13% respectively.

Discussion

This is the first study to compare the early treatment of septic shock between Indigenous and Non-indigenous patients. Despite being over-represented, Indigenous patients with septic shock presenting to the RDH ED in the Top End appear to receive the same standard of care as Non-indigenous patients; with no significant differences in compliance with the sepsis resuscitation bundle, ICU management and source control. Also, outcomes for Indigenous patients did not differ significantly with respect to LOS and mortality. This is despite the differing modes of arrival, likely delayed ED presentation, remoteness and higher chronic disease burden in Indigenous patients.

A delayed ED presentation for Indigenous patients with septic shock is suggested by the present study's findings of a higher proportion of aeromedical retrieval, lower self-presentation rate and a trend towards a higher rate of hypotension on arrival. The tyranny of distance for remote Indigenous communities in the Top End is the likely explanation for 38% of Indigenous patients requiring aeromedical retrieval. The need for retrieval would have incurred unavoidable delays to ED presentation and possible delays to optimal septic shock management. A lower self-presentation rate and a trend to more hypotension on arrival suggest that more Indigenous patients presented later after the onset of severe sepsis.

While there was no difference in compliance with the Surviving Sepsis resuscitation bundle, only 44% of all patients received antibiotics within the recommended 3 hours of presentation. Also, the mean time to antibiotics of 8.2 hours is longer than recommended by a large Canadian study which found that antibiotic administration within the first hour of septic shock was associated with a 79.9% survival to hospital discharge; falling by 7.6% for every hour of delay for the first six hours after onset of hypotension [13]. As explained above, the absence of EGDT at RDH is consistent with Australasian practice and is supported by the ANZICS position statement [6].

Although it has been suggested that an ED lead time > 4.5 hours may increase hospital mortality [7], this may not be the case in the present study, which had a mean ED lead time of 7.7 hours (with only 26% <4 hours). While ED lead time may be a surrogate measure of delay to appropriate treatment of septic shock, this may not be true for RDH. The high incidence of sepsis in the Top End [1] is likely to have resulted in a high level of expertise in the RDH ED. Therefore delays to ICU admission at RDH may not lead to suboptimal care of septic shock; as it is possible for all components of the resuscitation bundle to be implemented in the ED.

Pneumonia was the most common cause of septic shock in both groups, being consistent with previous studies in the Top End population [1,3]. The high proportion of patients requiring vasopressors, despite a mean fluid resuscitation of 2.4 litres, suggests a high proportion of patients had severe septic shock. This is supported by the ventilation rate of 35%, CRRT requirement in 26% and high APACHE II scores. The increased prevalence of chronic obstructive pulmonary disease, diabetes, end stage renal failure and hazardous alcohol use in Indigenous patients is likely to account for the similar APACHE II scores despite their younger age. Alternatively, more severe physiological disturbance, possibly explained by later presentation, could also account for this difference. The younger age, higher proportion of females and higher chronic disease burden in Indigenous patients is similar to that found in the large prospective sepsis study from the same population [1].

The overall rate of positive blood cultures of 40% is consistent with the reported rate of 30-50%[4]. While only 60% of blood cultures in the present study were taken prior to antibiotic administration this did not significantly reduce the chance of identifying a causative organism. This is an important finding which supports the practice of taking blood cultures even if antibiotics have already been administered.

Limitations

The present study is limited by its single-centre, retrospective design, relatively small numbers and missing medical records. Also, deaths occurring pre hospital or in the ED were not studied and therefore it is unknown how many of these were from septic shock. While this study was underpowered to investigate mortality, the ICU and hospital mortality of 8.5% and 13% respectively was

lower than expected. The lower mortality may be partly explained by the small numbers and missing medical records. The missing medical records may have introduced a selection bias, with deceased patients having harder to find records. However, without access to these records it is unknown how many would have met inclusion criteria (i.e. had community acquired septic shock). As has been discussed, the present study's cohort had very similar demographics to the larger prospective study from the same population [1]. This suggests that any selection bias introduced by the missing records affected both groups equally. Therefore, the present study's cohort is likely to be a representative sample for the purposes of comparing treatment between Indigenous and Non-indigenous patients with septic shock.

Conclusions

The standard of treatment for community acquired septic shock in the Top End of Australia does not appear to differ between Indigenous and Non-indigenous patients; including compliance with surviving sepsis resuscitation bundle, timely antibiotic therapy, intensive care therapies and source control. While this is encouraging, the contributing factors leading to a higher burden of sepsis and septic shock in Indigenous people in the Top End needs further investigation. The study's findings also support the taking of blood cultures in septic shock, even if antibiotics have already been administered.

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