EMA Emergency Medicine Australasia

Emergency Medicine Australasia (2023) **35**, 564–571 doi: 10.1111/1742-6723.14168

ORIGINAL RESEARCH

Introduction of an emergency medicine pharmacist-led sepsis alert response system in the emergency department: A cohort study

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Abstract

Objective: To determine effects of implementing a sepsis alert response system in the ED that included early intervention by emergency medicine (EM) pharmacists.

Methods: A prospective cohort (8 February 2016 to 28 February 2018) of patients after implementation of a sepsis alert response system in an Australian ED was compared to a retrospective cohort (3 January 2015 to 7 February 2016) of patients with sepsis who presented during EM pharmacist working hours and were admitted to the ICU.

Results: There were 184 patients, including 80 patients pre- and 104 patients post-implementation. The post-intervention cohort was triaged at a higher acuity, had higher quick Sepsis-related Organ Failure Assessment (qSOFA) scores and higher initial lactate measurements. After the intervention, antimicrobial agents were administered to patients within 60 min of presentation more often (21 [26.3%] to 85 [81.7%], $P < 0.001$). After adjusting for presenting triage category, admission lactate and presenting qSOFA scores, this association remained significant (adjusted odds ratio 9.99; 95% confidence interval 4.7–21.3). Significant improvements were observed for proportion of patients who had intravenous fluids initiated within 60 min (47.5% *vs* 72.1%); proportion of patients who had serum lactate measured within 60 min (50.0% *vs* 77.9%) and proportion of patients who had blood cultures performed within 60 min (52.5% *vs* 85.6%).

Conclusion: Implementation of a sepsis alert response that included early involvement of the EM pharmacist was associated with improvement in time to antimicrobials and other components of the sepsis bundle. An upfront, multidisciplinary approach to patients presenting to the ED with suspected sepsis should be considered more broadly.

Key words: *medicines management, pharmacists, sepsis.*

Key findings

- Introduction of an ED sepsis alert response driven by EM pharmacists improved time to antimicrobial administration for patients with sepsis requiring transfer to ICU.
- Improvements in the proportion of patients who received other components of the sepsis bundle of care within 60 min also improved post-intervention.
- An upfront, multidisciplinary approach with the inclusion of EM pharmacists in sepsis management should be considered.

Introduction

Early identification and management of patients with sepsis have been shown to improve outcomes.[1–3] The Surviving Sepsis Campaign guidelines for the treatment of patients with sepsis and septic shock recommend the initiation of broad-spectrum antimicrobials within 60 min of recognition. This is primarily driven by evidence demonstrating an association between timely antimicrobial administration and mortality in patients with septic shock.[3–6] In the ED, recognition of patients presenting with sepsis allows for timely initiation of the sepsis bundle of care. There are no other

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Accepted 19 December 2022

disease-modifying therapies for sepsis and septic shock besides timely antimicrobial administration and implementation of a sepsis bundle of care that have consistently been associated with improved outcomes.[7–9]

Compliance with timely antimicrobial administration for patients presenting with sepsis in the ED remains a challenge.[1,10] A number of factors have been identified as contributors to delays, including vague presenting symptoms, a lower acuity triage score, difficult intravenous access, deferred antimicrobial decision-making and prescribing and ED overcrowding.[1,10–13]

Emergency medicine (EM) clinical pharmacists are increasingly involved in the early management of critically unwell patient presentations.[14–19] The benefits of early involvement of the EM pharmacist in these scenarios are likely multifactorial with emerging evidence demonstrating improvements in time to medication prescribing and administration, and a reduction in medication errors.[12,15,20]

The implementation of sepsis performance improvement programmes which includes education, screening, measurement of sepsis bundle performance, patient outcomes and actions for identified opportunities is associated with better sepsis bundle performance and a reduction in mortality.[1]

The potential integration of the pharmacist into the sepsis alert response as routine care has not been thoroughly investigated. The EM pharmacist is uniquely positioned to improve sepsis performance. As recognised experts in antimicrobial stewardship, pharmacists can provide a comprehensive review of patient allergies, medical and medication history, previous microbiology cultures, and identify risk factors for multi-resistant pathogens. In addition, their thorough knowledge of medication administration may support efficient antimicrobial ordering and administration.

The aim of this study was to evaluate the impact of the introduction of a sepsis performance improvement programme in the ED which included the implementation of a sepsis alert response with early involvement of the EM pharmacist in an Australian adult major referral hospital.

Methods

Study design and setting

This was a pre-post interventional study, with the post-intervention cohort recruited prospectively between 8 February 2016 and 28 February 2018, compared to a retrospective cohort between 3 January 2015 and 7 February 2016.

The study was conducted at an adult major referral hospital in metropolitan Melbourne, Victoria, Australia with an annual attendance of approximately 70 000 patients. The Emergency and Trauma Centre (E&TC) is staffed by emergency physicians between 07.00–02.00 hours, Tuesday–Thursday, and 24 h a day, Friday–Monday. The hospital provides Victorian state services for major trauma, burns, haemophilia, cystic fibrosis, heart and lung transplants, HIV, adult haematological malignancies, and has one of Australia's leading intensive care units (ICUs), with capacity for advanced interventions including extracorporeal membrane oxygenation and more than 3000 ICU admissions per year.

Intervention

From 8 February 2016, a sepsis alert response system was introduced with the aim to improve time to administration of the sepsis bundle of care for patients presenting with sepsis, or suspected sepsis. The bundle of care includes taking a minimum of two sets of blood cultures, measuring a serum lactate, administering a bolus of intravenous fluid (250–500 mL) with more fluid as appropriate and intravenous antimicrobials in accordance with the Surviving Sepsis Campaign, national and hospital guidelines.[1,21]

Pre-arrival notification and early communication at triage of all patients presenting with suspected sepsis were delivered to all members of the sepsis alert team. The members of the sepsis alert team include the primary nurse, nurse-in-charge, emergency physician and registrar and the EM pharmacist. Education to medical and nursing staff around sepsis recognition, the sepsis alert response and timely administration of the sepsis bundle of care was conducted prior to implementation, and regularly throughout the post-intervention period. The EM pharmacists attending sepsis alerts have at least 2 years of clinical experience and are required to complete formal training prior to involvement. Successful sepsis credentialing includes completion of an in-house online sepsis module for pharmacists, the Partnered Pharmacist Medication Charting (PPMC) credentialing,[22] Therapeutic Drug Monitoring of Aminoglycosides and Vancomycin credentialing[23] and Stroke thrombolysis credentialing.[17]

A hospital-wide programme for monthly auditing of time to completion of the sepsis bundle of care was implemented in February 2016 with a focus on the E&TC and inpatient units. Results were reviewed at a dedicated sepsis working group meeting with representation from the hospital executive, ICU, EM, inpatient medical and nursing teams as well as antimicrobial stewardship and relevant senior pharmacists. The working group identified barriers and solutions to completion of the sepsis bundle, established a hospital sepsis guideline that included consensus agreement on empiric antimicrobials for common sepsis presentations and provided monthly feedback to the E&TC and inpatient units on sepsis bundle performance both during pharmacist working hours and after hours.

The local consensus-based criteria for activation of a sepsis alert in the E&TC requires a patient to have known or suspected infection with two or more of the following: oral temperature <36°C or >38°C or core temperature <36.4°C or >38.4°C, heart rate >95/min, respiratory rate >22 breaths per minute, systolic BP <100 mmHg, change in mental status or white cell count <4 or $>12 \times 10^9$/L. Other risk factors include neutropenia or recent chemotherapy.

The EM pharmacist responds to all sepsis alerts immediately upon activation. Specific responsibilities in the sepsis alert are to facilitate rapid bedside decision-making and prescribing of empiric antimicrobials after discussion with the treating

doctor on suspected source of infection and determination of previous medication allergies and microbiology cultures, and any relevant past medical history and medications. Prescribing of empiric antimicrobials is performed either directly by the pharmacist via the PPMC model of care[22] or medical staff in the sepsis alert. The PPMC model is an alternative to medical prescribing. It involves a credentialed pharmacist taking an early medication history, having a face-to-face discussion with the treating medical staff about the current medical and medication-related problems following which a medication management plan is agreed upon. Appropriate medications are then charted by the pharmacist on the inpatient medication record from which nurses administer medications.

The pharmacist also assists with rapid access to and drawing up appropriate antimicrobials for immediate administration by the primary nurse. Other components of the sepsis bundle (taking two sets of blood cultures, measuring a serum lactate and administering an intravenous fluid bolus) are also expedited by the EM pharmacist.

Selection of participants

The post-intervention cohort was identified prospectively until the required sample size was reached. All patients who presented to the E&TC, had a sepsis alert activated on arrival and were admitted to ICU during the study period with sepsis within EM pharmacist working hours (07.00–21.00 hours, 7 days a week) were included. Patients were excluded if no sepsis alert response was activated, if antimicrobials were given pre-arrival, or if patients deteriorated and developed sepsis after arrival in the E&TC (Fig. 1). The pre-intervention (comparator) consisted of a retrospective cohort containing all patient presentations to the E&TC with sepsis or septic shock requiring transfer to ICU and identified via the Australian and New Zealand Intensive Care Society (ANZICs) database coding between EM pharmacist working hours. The cohorts were restricted to patients admitted to ICU as, presumably, these patients have the greatest benefit from early intervention with the sepsis bundle of care.

All data for both arms were extracted and calculated retrospectively using explicit medical record review by a research assistant who was not part of the study team. A random sample of 10% of records were verified by a study investigator. Exposure variables included patient baseline characteristics such as age, sex, past medical history, Australasian Triage Scale (ATS) category, presumed initial source of infection and associated quick Sepsis-related Organ Failure Assessment (qSOFA) score.[24]

Outcomes

The primary outcome was the proportion of patients who received antimicrobials within 60 min of arrival to the E&TC. Time of arrival was defined as the time of patient registration. Administration time was defined as the time the first antimicrobial medication prescription was signed off by the administering nurse on the patients' medication chart, implying that the medication was administered at that time. Secondary outcomes were time to antimicrobial administration, proportion of patients receiving each of the remaining components of the sepsis bundle of care within 60 min of arrival (intravenous fluids, two sets of blood cultures and a serum lactate), and the proportion receiving the entire bundle of care within 60 min of arrival (intravenous fluids, two sets of blood cultures, a serum lactate and empiric antimicrobials). The proportion of patients who were prescribed empiric antimicrobials by the EM pharmacist post-intervention, median length of stay in the E&TC, ICU and hospital, as well as death at hospital discharge were reported.

Analysis

The sample size calculation was based on previous local data demonstrating 26% of ICU patients with sepsis received antimicrobials within 60 min of presentation to the E&TC. A target of 50% of patients receiving antimicrobials within 60 min of presentation was considered a clinically significant improvement. With 80% power and an alpha of 0.05, 77 patients were required in each arm. Continuous data were summarised using means and standard deviation if near-normally distributed, or medians with interquartile range (IQR) if skewed. Categorical variables were summarised using proportions.

The primary outcome variable was reported using odds ratio (OR) and adjusted OR (aOR) with 95% confidence intervals (CIs). The association between the intervention and primary outcome was adjusted for differences in baseline characteristics between the cohorts using multivariable logistic regression. Time to antimicrobial administration was displayed using a Kaplan–Meier survival graph.

A P value of <0.05 was defined to be statistically significant. All analyses were performed using Stata v15.0 (StataCorp, College Station, TX, USA).

The study protocol was reviewed and approved by The Hospital Research and Ethics Committee (Project ID 505/16).

Results

There were 184 patients included for analysis with 104 patients included after intervention, and 80 patients were in the pre-intervention comparator arm (Fig. 1). Additional patients were included to allow for loss of patients based on the exclusion criteria (Fig. 1). The cohorts were similar for baseline characteristics such as age, sex, and co-morbidities, but not for serum lactate, qSOFA and triage category (Table 1). There were a total of 30 individual pharmacists trained and involved in sepsis alerts activated in the intervention arm.

The proportion of patients who received empiric antimicrobials within 60 min of arrival improved from 21 (26.3%) to 85 (81.7%) ($P < 0.001$) patients post-intervention (OR 12.6, 95% CI 6.2–25.4). After adjusting for presenting triage category, admission lactate and presenting qSOFA scores, this association remained significant (aOR

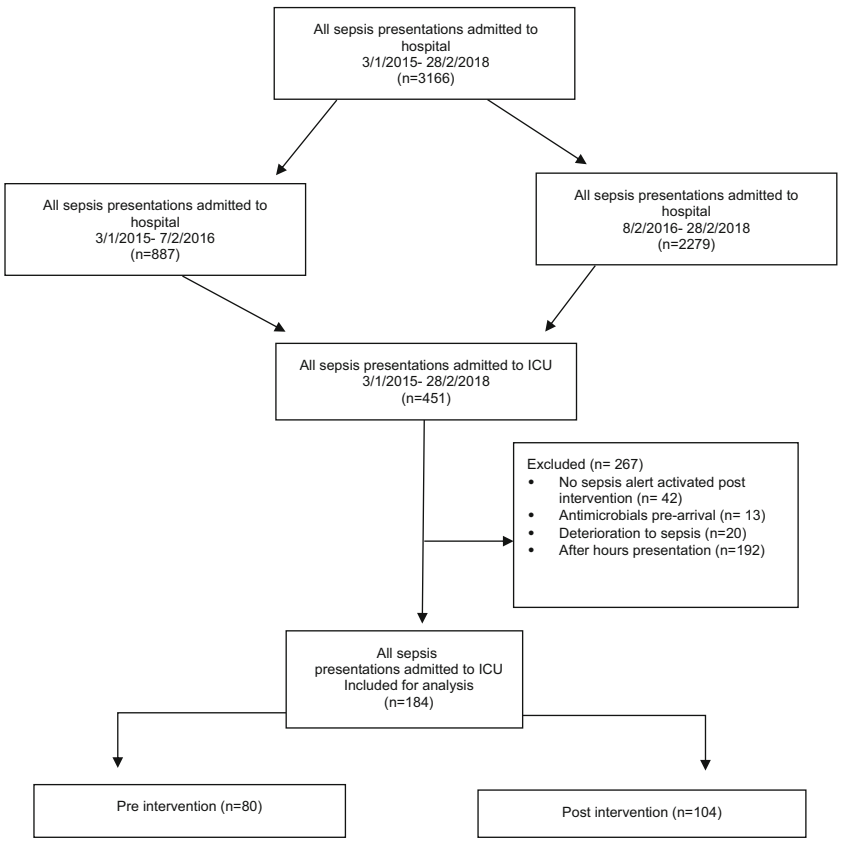

Figure 1. *Inclusion and analysis flow chart for patients with sepsis.*

9.99, 95% CI 4.7–21.3; Appendix S1). The median time to antimicrobials was 91 min (IQR 59.5–163.5) and 38 min (IQR 27–54) pre- and post-intervention ($P < 0.001$) (Table 2). A comparison of time to antimicrobial administration between the two periods is illustrated in Figure 2.

The proportion of patients who received the individual components of the sepsis bundle of care within 60 min significantly improved post-intervention: intravenous fluids (47.5% *vs* 72.1%; $P = 0.002$), blood cultures (52.5% *vs* 85.6%; $P < 0.001$), serum lactate (50.0% *vs* 77.9%; $P < 0.001$). The proportion of patients who had all four components of the sepsis bundle of care significantly improved post-intervention, 8 (10.0%) *versus* 52 (50.0%) ($P < 0.001$). There was no significant difference in median length of stay in E&TC, ICU or hospital. Death at hospital discharge did not change post-intervention (Table 2).

The EM pharmacist attended all sepsis alerts activated during working hours in the intervention arm and prescribed antimicrobials in 28 patients (27%) via the PPMC model of care. In the post-intervention period, when the pharmacist prescribed antibiotics, 25 (89.3%) patients received antibiotics within 60 min compared to 60 (79%) when antibiotics were prescribed by medical practitioners ($P = 0.23$). Median times to antibiotics being prescribed by pharmacists was 34.5 min (IQR 26–49.5) and 40 min (IQR 27–57) when charted by medical practitioners ($P = 0.36$).

Discussion

Following introduction of a sepsis alert response system driven by the EM pharmacist, significant improvements were observed in time to antimicrobial administration and other components of the sepsis bundle of care. A multidisciplinary approach to assessment and management of patients with suspected sepsis is therefore indicated.

The improvements align with recent recommendations from the first Australian Commission on Safety and Quality in Health Care Sepsis Clinical Care Standard and the Surviving Sepsis Campaign[25] and the Australian Commission on Safety and Quality in Health Care National Sepsis Program for patients with septic shock[1] suggesting these results are feasible and achievable through structured programmes. Furthermore, the proportion of patients who received empiric antimicrobials and the sepsis bundle of care within 60 min of presentation was higher than results reported from sepsis improvement programmes which did not include a pharmacist from 97 Australian EDs where the proportion of patients who received empirical antibiotics within 60 min of triage or recognition of sepsis improved from 29.3% to 52.2%.[26]

These findings are consistent with those based in North America by Weant *et al.* who were the first to report on EM pharmacist roles of providing dosing advice for empiric antimicrobials in the ED.[27] Furthermore, Moussavi *et al.* showed involvement of an EM pharmacist in patients with sepsis admitted to ICU was associated with reductions in administration time for antibiotics (median 0.61 *vs* 0.88 h; $P = 0.001$) and initial antibiotics were more often appropriate.[28] Similarly, Yarbrough *et al.* reported an improvement in time to completion of the 3 h bundle (51 min *vs* 71 min; $P = 0.013$) when a pharmacist was present in ED sepsis alerts.[29] This is the first Australian sepsis alert response that includes an EM pharmacist. Our model of care also includes a system-wide approach incorporating regular education, monthly auditing, and feedback.

The EM pharmacist's presence at a sepsis alert enables advocacy for timely and appropriate initiation of antimicrobials. The EM pharmacist could be dedicated to investigation of the most appropriate antimicrobial options based on patient history,

TABLE 1. *Baseline characteristics of ED patients with sepsis transferred to ICU*

	Pre-intervention ($n = 80$)	Post-intervention ($n = 104$)	*P*-value
Age, years, mean (SD)	60.1 (15.5)	59.7 (17.0)	0.86
Sex, *n* (%)			0.96
Male	48 (60)	62 (59.6)	
Female	32 (40)	42 (40.4)	
Initial presumed infection source, *n* (%)			0.043
Respiratory	43 (53.8)	38 (36.5)	
Extremities	4 (5.0)	7 (6.7)	
Abdominal	2 (2.5)	6 (5.8)	
Urinary tract	10 (12.5)	6 (5.8)	
Central nervous system	3 (3.8)	3 (2.9)	
Other	1 (1.3)	6 (5.8)	
Unknown	17 (21.3)	38 (36.5)	
Australasian Triage Scale, *n* (%)†			0.001
1	7 (8.75)	6 (5.8)	
2	38 (47.5)	78 (75.0)	
3	33 (41.3)	18 (17.3)	
4	2 (2.5)	2 (1.9)	
Systolic blood pressure (mmHg)			
On arrival, mean (SD)	109.9 (29.7)	108.7 (27.2)	0.77
Lowest in ED, mean (SD)	87.9 (21.7)	86.0 (19.2)	0.18
Respiratory rate			
On arrival, mean (SD)	25.0 (7.9)	27.8 (8.3)	0.02
Glasgow Coma Scale, median (IQR)	15 (14–15)	15 (14–15)	0.75
Presenting serum lactate (mmol/L), mean (SD)	2.6 (2.0)	3.7 (2.2)	0.003
Presenting qSOFA score, median (IQR)	1 (1–2)	2 (1–2)	0.019
Past medical history, *n* (%)			
COPD/asthma	19 (23.7)	30 (30.6)	0.31
Heart failure	12 (15.0)	7 (7.1)	0.09
End stage renal failure	6 (7.5)	4 (4.1)	0.32
Intravenous drug use	11 (13.7)	11 (11.2)	0.33
HIV	3 (3.7)	2 (2.0)	0.91
Malignancy	18 (22.5)	17 (17.3)	0.39
Organ transplant	7 (8.7)	6 (6.1)	0.50
Nursing home resident, *n* (%)	3 (3.7)	3 (3.1)	0.99

†Australasian Triage Scale is a clinical tool used to establish the maximum waiting time for medical assessment and treatment in the ED, from category 1 which requires immediate simultaneous assessment and treatment to category 5, a chronic or minor condition which can be assessed and treated within 2 h. COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; IQR, interquartile range; qSOFA, quick Sepsis-related Organ Failure Assessment; SD, standard deviation.

allergies, and previous microbiology, whereas the remaining team can focus on initial patient history taking, examination, intravenous access and initiation of fluid resuscitation and urgent investigations. Indeed, as medication experts, the EM pharmacist is well placed to make antimicrobial recommendations in accordance with national and local guidelines, thus ensuring that treatment options are also aligned with antimicrobial

TABLE 2. *Primary and secondary outcomes of ED patients with sepsis transferred to ICU*

	Pre-intervention ($n = 80$)	Post-intervention ($n = 104$)	*P*-value
Antibiotics within 60 min, *n* (%)†	21 (26.3)	85 (81.7)	<0.001
Median time to antibiotics (IQR)	91 (59.5–163.5)	38 (27–54)	<0.001
Intravenous fluids within 60 min, *n* (%)	38 (47.5)	75 (72.1)	0.002
Serum lactate within 60 min, *n* (%)	40 (50.0)	81 (77.9)	<0.001
Blood cultures			
Within 60 min, *n* (%)	42 (52.5)	89 (85.6)	<0.001
Before antibiotics, *n* (%)	60 (75.0)	71 (68.9)	0.37
All four indicators within 60 min, *n* (%)	8 (10.0)	52 (50.0)	<0.001
LOS in ED, median hours (IQR)	6 (4–8)	6 (5–8.5)	0.45
LOS in ICU, median hours (IQR)	82.5 (40–120)	82 (50.5–143.5)	0.24
Death at hospital discharge, *n* (%)	9 (11.2)	15 (14.4)	0.27
LOS in hospital, median (IQR)	234.5 (142–463)	269.5 (162.5–487.5)	0.36

†Primary outcome. IQR, interquartile range; LOS, length of stay.

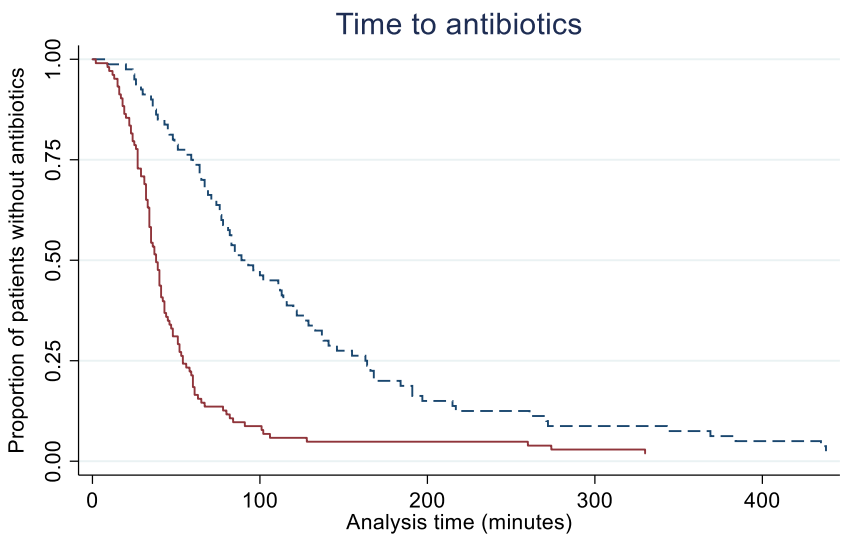

Figure 2. *Kaplan–Meier for time to antibiotics. (----), Pre-intervention; (——), post-intervention.*

stewardship principles. Although not assessed in the present study, this is consistent with previously published evidence surrounding EM pharmacists from North America and Australia.[27,28,30,31]

A unique feature of the intervention was that all pharmacists were credentialed to prescribe empiric antimicrobials in consultation with medical staff, which occurred in 30% of patients via the PPMC model of care. PPMC is an alternative to individual medical prescribing for hospitalised patients. It has been shown to reduce the rate of medication errors.[22] Early prescribing may contribute to improved time to medication administration; however, the present study was not powered to detect a difference in time to prescribing by pharmacists compared to medical practitioners.

The criteria for activation of a sepsis alert locally have similarities with previously published data for activation of sepsis response systems.[32,33] A deliberate decision was made to avoid limiting the alerts to only patients with organ dysfunction in order to capture a broader group of patients identified at triage using basic clinical parameters. This group of patients may subsequently be identified as having organ dysfunction or may deteriorate and develop sepsis while in the ED. Using this approach led to activation of sepsis alerts for patients who eventually did not require an ICU admission – whether this was because of the sepsis alert system and aggressive early intervention remains to be determined. A formal process for standing down sepsis alert activations that did not require urgent antibiotics was developed to ensure sustainability of the programme. This included discussion with the emergency physician, EM pharmacist and treating doctor and was documented in the patient's medical record by the EM pharmacist. Regular audits indicate most patients with a sepsis alert activated in the E&TC have a final diagnosis of infection.

Many EDs have adopted automated systems within electronic medical records that alert clinicians of potential sepsis and in some cases this can also trigger electronic sepsis care

pathways.[25,34] Our sepsis alert response was developed prior to the introduction of electronic medical records and has been maintained as a manual process of activation based on clinical judgement. Automation of the sepsis response in addition to the use of the current manual activation process is a challenging balancing act between alert fatigue and identifying additional patients with sepsis, as many of the automated systems have high sensitivity but low specificity.

Despite both cohorts of patients having similar demographics, comorbidities and source of sepsis, there was imbalance between the cohorts with regards to ATS category, qSOFA scores and initial serum lactate measurements. We postulate that these observed differences could have been an effect of improved education and recognition of sepsis, rather than differences in patient cohorts. Allocation of higher ATS categories for suspected sepsis has been previously suggested.[11] Similarly, observation of higher serum lactate could be a reflection of reduced time to lactate measurements. However, it is also possible that patients in the intervention arm may have been more unwell as demonstrated in the higher qSOFA score, higher acuity triage category and serum lactate.

Limitations

Several limitations must be acknowledged. This was a single-centre study using retrospective data to collect the primary and secondary outcomes. The introduction of hospital-wide monthly auditing on sepsis performance, education, as well as specific training of the EM pharmacists or the sepsis alert itself may have had a direct impact in the results, but this was difficult to adjust for. It is possible that the results may have less external validity and generalisability. In addition, there was potential for selection bias because of EM pharmacist availability to only attend sepsis alerts during working hours. The post-intervention cohort was restricted to patients who had a sepsis alert. Delayed recognition of sepsis is a major contributor to worse outcomes and this cohort could have been biased towards better outcomes through early recognition. However, all patients included in the present study were admitted to the ICU, reflecting high disease severity. The improvements observed in the present study reflected the entire bundle of care, rather than any individual component.

Future research should aim to examine the impact of such a model of care across all patients including those not requiring ICU admission and in multiple centres in a prospective study, powered to detect a difference on mortality and length of stay.

Conclusion

Implementation of a sepsis alert response that included early involvement of the EM pharmacist was associated with improvement in time to antimicrobials in the ED. An upfront, multidisciplinary approach with the inclusion of EM pharmacists in the management of patients with sepsis could be considered as part of standard patient care.

Acknowledgements

The authors would like to acknowledge the assistance provided by research assistant Ria Hopkins with data collection for the present study. The authors also acknowledge the Emergency and Trauma Centre and individual pharmacists who supported the implementation of this study.

Author contributions

CPR: Conceptualisation, data curation, investigation, methodology, project administration, validation, visualisation, writing – original draft, writing – review and editing. MD: Conceptualisation, investigation, methodology, supervision, validation, visualisation, writing – original draft, writing – review and editing. AN: Investigation, methodology, validation, visualisation, writing – original draft, writing – review and editing. MS: Investigation, methodology, validation, visualisation, writing – original draft, writing – review and editing. SM: Investigation, methodology, supervision, validation, visualisation, writing – original draft, writing – review and editing. CL: Conceptualisation, investigation, methodology, validation, visualisation, writing – original draft, writing – review and editing. BM: Conceptualisation, formal analysis, investigation, methodology, supervision, validation, visualisation, writing – original draft, writing – review and editing.

Competing interests

BM is a section editor for *Emergency Medicine Australasia* and was excluded from all editorial decision-making related to the acceptance of this article for publication.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site:

Appendix S1. Variables associated with antibiotics within 60 min.