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Blood Culture Ordering After Sepsis Alerts and Subsequent Patient Outcomes: An Electronic Health Record-Based Study

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Abstract. Sepsis is a global health priority associated with high mortality. Clinical decision support systems have been developed to support clinicians with sepsis management. Ordering blood cultures (BCs) for suspected sepsis patients are strongly recommended by clinical guidelines. However, limited evidence exists investigating BC ordering following sepsis alerts and subsequent patient outcomes. This study aimed to investigate this issue using electronic health record data from an acute care hospital in Australia. Of 4,092 patients, only 16.6% had a BC ordered following a sepsis alert. The median time from the first sepsis alert to a BC order was 15.3 hours. Patients had 5.89 times higher odds of being diagnosed with sepsis if a BC was ordered following a sepsis alert than those without BC ordered ($p<0.0001$). Further investigation is needed to understand reasons behind the delay or failure to order a BC despite receiving electronic sepsis alerts and how decision support can be optimized to improve patient outcomes.

Keywords. Sepsis, computerized clinical decision support, blood culture, antibiotics appropriateness

1. Introduction

Sepsis remains one of the deadliest conditions in the world despite recent scientific and therapeutic advances. It is of great clinical importance, being responsible for more than a third of all hospital admissions, and approximately half of all intensive care unit (ICU) admissions [1]. The most recent sepsis definition, the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), defines sepsis as "a life-threatening organ dysfunction due to a dysregulated host response to infection" [2]. Sepsis can develop from a diverse range of microorganisms [3]. Current guidelines recommend taking two sets of blood cultures (BCs) prior to the administration of empiric antibiotics when sepsis is suspected [4; 5]. The laboratory will attempt to culture and identify the

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sepsis-causing organism. Further susceptibility testing allows the provision of targeted antibiotic therapy [4-6]. Timely BC collection to identify pathogenic bacteria, followed by prompt administration of appropriate therapeutic antibiotics and source control, is recommended for the improvement of patient outcomes [4; 5; 7-9]. Early detection of sepsis facilitates earlier involvement of senior clinicians to confirm the sepsis diagnosis and support prompt treatment with appropriate intravenous antibiotics and fluids. Computerized clinical decision support (CCDS) systems have been developed to improve early sepsis detection in hospital [10; 11]. CCDS systems provide a valuable mechanism for incorporating sepsis recognition algorithms, which automatically generate alerts and provide decision support to guide appropriate, prompt treatment, into the hospital environment. Limited evidence exists on BC ordering following a sepsis alert and the associated impact on patient diagnosis and outcomes. This study aimed to 1) examine the rate and timing of BC ordering following a sepsis alert and 2) investigate the association between BC ordering and patient adverse outcomes.

2. Methods

2.1. Study Design, Population and CCDS System

This was a retrospective cohort study utilising data extracted from electronic health record (EHR) systems. We included adult patients (aged 18 and over at the time of admission) admitted to an acute teaching hospital in Sydney from Dec 2014 to June 2016. The hospital is a 570-bed tertiary urban hospital with 24,500 inpatient admissions annually. An automated sepsis alert system, the Modified St. John Rule, was implemented to provide warnings for suspected sepsis cases during the study period. This system was developed by NSW eHealth in partnership with the Clinical Excellence Commission (CEC) in New South Wales, Australia. It was an updated version of the St. John Sepsis Surveillance Agent (Cerner) and included additional clinical criteria for activating a sepsis alert [12; 13]. We included patients who had at least one sepsis alert. Patients were excluded if they had a BC before a sepsis alert or a principal diagnosis of pregnancy and/or childbirth. Ethics approval was provided by the Macquarie University Human Research Ethics Committee (Reference No: 5201600265).

2.2. Data Sources and Analysis

Patient demographic data and admission related data, including data on BC ordering and sepsis alerting, were extracted from different EHR systems. BCs and sepsis alerts were time-stamped. Data sets from different sources were linked using de-identified medical record numbers and related time stamps. Sepsis diagnoses were identified using International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) codes. Sepsis codes were from the Classification of Hospital Acquired Diagnoses (CHADx) [14]. To examine the rate and timing of BC ordering following a sepsis alert (Aim 1), we divided patients into two patient groups: 1) BC following an alert, and 2) no BC following an alert. Time intervals between the first alert and the first BC order time was calculated by patient groups. Cumulative proportions of patients with a BC ordered after the first alert are presented. Logistic regression modelling was applied to investigate the association between BC ordering and patient adverse outcomes, including sepsis diagnosis, ICU admission, and

in-hospital mortality (Aim 2). Relevant patient demographic and clinical information, including age, sex, diabetes status, and Charlson comorbidity index (CCI) were adjusted for in the models. Data linkage and analyses were performed using SAS (version 9.4).

3. Results

3.1. BC Ordered Following the First Sepsis Alert

A total of 36,065 patient admissions were recorded during the study period, of which 4,092 patients had a sepsis alert and were eligible for inclusion in this study. A total of 8,222 sepsis alerts were triggered for these patients. Of patients with an alert, 16.6% (n=679) had a BC ordered after the first sepsis alert was triggered while 83.4% (n=3,413) had no BC ordered (Table 1). Patients with a BC ordered had a higher median CCI than those without. Where a BC was ordered following an alert, 50% were ordered within 15.3 hours of the first alert triggered, however, the interquartile range (IQR) varied from 2.8 hours to 70.8 hours. Figure 1 shows the cumulative proportion of the first BCs ordered within 6 hours after the first alert, where only a small proportion (5.7%, n=235) of patients had BCs ordered.

Table 1. Patient characteristics by patient group

Characteristics	Patient group		Overall, N=4,092
	BC following an alert, N=679	Alerted, no BC, N=3,413	
Age, mean (SD)	67.0 (17.4)	66.5 (18.3)	66.6 (18.2)
Male, N (%)	335 (49.3)	1664 (48.8)	1999 (48.9)
Diabetes, N (%)	298 (43.9)	1262 (37.0)	1560 (38.1)
CCI, Median (IQR)	2 (0-4)	1 (0-3)	1 (0-3)

BC: blood culture; IQR: interquartile range; CCI: Charlson comorbidity index

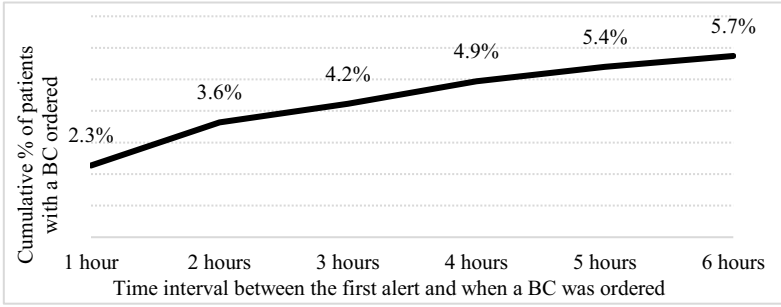

Figure 1. Cumulative percentage of patients with a blood culture (BC) ordered after the first alert by alert type (Percentage was calculated out of patients who an alert during hospital stay. Time intervals longer than 6 hours were trimmed)

3.2. BC Ordering and Patient Outcomes

When a BC was ordered following an alert, one third of patients (32.4%=220/679) were diagnosed with sepsis while only 7.5% of patients (257/3413) were diagnosed with sepsis if there was an alert but no BC ordered (Table 2). Of the 257 patients who had both an alert and a sepsis diagnosis, but no BC, 25% (n=65) were admitted to ICU and 14%

(n=36) died in hospital. Overall, patients were 5.89 times more likely to be diagnosed with sepsis if a BC was ordered following a sepsis alert than those who received an alert, but no BC ordered (Odds ratio[OR]: 5.89, 95% CI: 4.80-7.22; p<0.0001). Although these patients with a BC were 3.24 times more likely to be admitted to an ICU than those without a BC (OR: 3.24, 95% CI :2.62-4.01; p<0.0001), there was no evidence of difference in mortality between the two groups (OR: 1.33, 95% CI: 0.95-1.84; p=0.1).

Table 2: Patient outcomes for patients with a sepsis alert by patient group.

Patient groups	Sepsis diagnosis	Total	Admitted to ICU N (row %)	In hospital Mortality N (row %)
BC following an alert	No	459	111 (24.2)	34 (7.4)
	Yes	220	113 (51.4)	29 (13.2)
No BC following an alert	No	3,156	265 (8.4)	148 (4.7)
	Yes	257	65 (25.3)	36 (14.0)

4. Discussion

Sepsis alerts from CCDS systems were designed to support early detection of sepsis and to facilitate the prompt involvement of senior clinicians. Following sepsis alerts, relevant clinical actions should be followed. This study found that only 16.6% of patients had a BC ordered after a sepsis alert despite clinical guidelines strongly recommending ordering two sets of blood culture for suspected sepsis patients [5]. Patients diagnosed with sepsis and receiving a sepsis alert, but no BCs, had a high mortality rate (14.0%). In addition, less than 6% of BCs were ordered within 6 hours of the first sepsis alert. These results are concerning given that timely BC followed by appropriate antibiotics are crucial for sepsis patient outcomes [15]. Further investigation is needed to understand the reasons behind this delay in BC ordering and low BC ordering rate. The high number of alerts generated for patients who did not have sepsis may have contributed to alert fatigue, which should be considered. The adoption of CCDS requires close attention to determine the specificity and sensitivity of sepsis alerting to avoid the increasingly recognized problem of alert fatigue [13; 16; 17].

Strengths of this study include utilization of a large EHR dataset, which consists of extensive laboratory, sepsis alert and admission data, allowing us to compare timing of sepsis alerts and BC ordering. This process would be extremely time- and resource-intensive to complete using other approaches, such as medical chart review. This study is limited by the lack of information on treatment (e.g., timing and appropriateness of antibiotics), and hospital capacity (e.g., adequacy of clinical staffing).

5. Conclusions

Sepsis remains a significant global health problem. This study has contributed to the knowledgebase on blood culture ordering and sepsis diagnosis following a sepsis alert, which has important implications for subsequent appropriate antibiotics administration and patient survival. Future studies focusing on why guidelines are or are not followed after a CCDS alert will benefit future CCDS implementation and potentially improve clinical workflow and patient outcomes.

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