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Impact of time to first antimicrobial dose on length of stay and 30-day hospital readmission in patients with lower limb cellulitis

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ABSTRACT

Objectives: There have been efforts to promote timely antimicrobial administration for patients with sepsis, but the importance for other infections is uncertain. This study analysed whether time to first antimicrobial dose (TFAD) in patients with lower limb cellulitis influenced outcome measures such as acute length of stay (LOS) in hospital and 30-day hospital readmission rates for cellulitis.

Methods: Medical records of patients admitted with lower limb cellulitis or erysipelas over a 15-month period (1 May 2019 to 30 November 2019 and 1 March 2020 to 31 October 2020) were reviewed. Patients requiring intensive care unit (ICU) admission were excluded. The TFAD was the difference (in minutes) between the emergency department triage time and the time that the antimicrobial was first recorded as administered. Analysis included log-transformed linear regression (for LOS) and logistic regression (for 30-day readmission with cellulitis), controlling for confounders where possible.

Results: The study included 282 patients with lower limb cellulitis. The median TFAD was 177 min (interquartile range, 98–290 min). Linear regression suggested a weak association between TFAD and LOS ($P = 0.05$; adjusted $R^2 = 0.01$), which was non-significant after adjusting for confounders ($P = 0.18$). There were too few patients readmitted within 30 days with cellulitis for meaningful analysis.

Conclusion: After controlling for confounders, no association between increased TFAD and increased acute LOS was identified for patients with lower limb cellulitis who did not require ICU admission (i.e. without septic shock). Conclusions could not be made for 30-day readmission rates for cellulitis.

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1. Introduction

A recent narrative review concluded that a delay in administration of antimicrobial therapy for 4–8 h while waiting for diagnostic results was not unreasonable as it was unlikely to be asso-

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ciated with significant adverse events for most common bacterial infections (with the exception of probable/confirmed septic shock or bacterial meningitis) [1]. A major limitation of that review was the absence of any randomised or observational study data on the impact of delayed antimicrobial therapy for skin and soft-tissue infections such as cellulitis [1].

A bundle of care for management of lower limb cellulitis was developed and implemented in three regional hospitals in Victoria, Australia, to see whether it could improve the appropriateness of antimicrobial therapy for cellulitis. The bundle guided medical and nursing staff towards key management priorities, e.g. leg elevation, appropriate antimicrobial selection, dosing and duration, and checking skin integrity. Metrics were collected on outcomes of care, including the time to first antimicrobial dose (TFAD), acute length of stay (LOS) in hospital, and 30-day readmission rates with cellulitis. The aim of this study was to explore whether any association between TFAD and clinical outcomes for patients with lower limb cellulitis could be demonstrated.

2. Methods

Adults with ICD-10-AM codes for lower limb cellulitis or erysipelas admitted to the three regional hospitals over a 15-month period (1 May 2019 to 30 November 2019 and 1 March 2020 to 31 October 2020) were identified. The two time periods represent baseline and post-intervention data collection periods for the lower limb cellulitis management plan.

Patients were excluded if they were not prescribed an antimicrobial at all or if cellulitis developed after admission because TFAD could not be calculated. Patients requiring admission to the intensive care unit (ICU) were excluded because the importance of early antimicrobial administration is already well accepted in those in whom cellulitis is accompanied by sepsis. Patients transferred directly to another facility were excluded because outcomes could not be ascertained. Those who had already contributed data to the study were also excluded. Demographic and clinical data (known co-morbidities, vital signs at presentation) were collected from the medical record by trained researchers using a standardised data collection form.

The triage time at the emergency department or urgent care centre and the time that the first antimicrobial dose was administered were both retrieved from the medical record. The TFAD was considered the difference (in minutes) between these two time points. The patient administration system provided the LOS (acute admission only, inclusive of parenteral therapies administered at home) and whether the patient was readmitted to the same hospital with cellulitis within 30 days of discharge. Descriptive and inferential statistics were derived using Stata® v.16.1 (StataCorp LLC, College Station, TX, USA). The median and interquartile range (IQR) were calculated for TFAD and LOS, and $\log_2$ transformations were performed prior to undertaking linear regression. An adjusted analysis controlling for known confounders of LOS for cellulitis (age >60 years and clinical features at presentation including tachycardia, hypotension, leukocytosis, elevated serum creatinine, obesity and diabetes mellitus) was performed [2]. Logistic regression was undertaken to explore the relationship between TFAD ($\log_2$ transformed) and 30-day readmission with cellulitis. This study was approved by the Ballarat Health Services and St John of God Human Research Ethics Committee.

3. Results

Data for TFAD was available for 282 patients with lower limb cellulitis over the 15-month period. Demographic and clinical information is provided in Table 1. The median TFAD was 177 min (IQR, 98–290 min). The TFAD was within 4 h in 67.7% (191/282) of patients. The median LOS for patients with lower limb cellulitis was 3 days (IQR, 1–5 days). Fourteen patients (5.0%) were readmitted to the same hospital with cellulitis within 30 days of discharge. There were no deaths.

Linear regression predicted that an increased TFAD would produce an increased acute LOS ($P = 0.05$; adjusted $R^2 = 0.01$). However, after controlling for known confounders (Table 1, excluding hypotension owing to low numbers), the relationship became non-significant ($P = 0.18$; adjusted $R^2 = 0.21$). There were too few patients readmitted within 30 days with cellulitis for meaningful analysis.

4. Discussion

The current study found a weak association between increased TFAD and increased acute LOS. After controlling for confounders, this association became non-significant. These data suggest that in a clinically stable patient, if the diagnosis is uncertain, taking the time to eliminate cellulitis mimics before prescribing antimicrobials will not impact an outcome such as LOS. Antimicrobial treatment should still be started promptly once the diagnosis is made. The low numbers of patients readmitted with cellulitis within 30 days of discharge meant that conclusions could not be reached about the relationship with TFAD.

The paucity of studies exploring the impact of TFAD may reflect the significant heterogeneity in clinical outcomes reported for cellulitis [3]. Mortality is clearly the gold standard, and in some infectious diseases such as sepsis, commencing antimicrobials within 60 min has been associated with a survival benefit [1,4]. Given this, the current study excluded patients requiring ICU admission as this is the group in whom cellulitis is accompanied by sepsis and the importance of early antimicrobial administration is already well accepted. Cellulitis has a mortality rate estimated at 1%, with an even lower attributable mortality [5]. This poses a challenge for achieving an adequately powered sample. As an example, the finding from an Australian study that a delay of longer than 8 h in administering empirical antimicrobials was independently associated with increased mortality in cellulitis ($P = 0.036$) was based on a sample of only 10 patient deaths accumulated over an 8-year period [6]. Both the statistical power and the robustness of the conclusions from this study over such a long time period were considered serious limitations [6]. The rigour of even large cohort studies attempting to explore the impact of TFAD on mortality outcomes for other conditions such as community-acquired pneumonia (CAP) has been criticised [7].

The challenges with mortality as an outcome measure for cellulitis mean that common surrogate measures such as LOS and readmission are often considered instead. These measures are known to have a range of confounding factors [8], some of which can be challenging to adjust for in analysis. An obvious confounder is disease severity. Unlike conditions such as CAP with a validated severity score (e.g. CORB) [4], there is no universally accepted method to determine the severity of cellulitis. While classifications such as those proposed by Eron et al. [9] are available, clinical uptake of these scoring approaches is limited [10]. This suggests that further research on the clinical utility and uptake of such cellulitis severity scales would be valuable.

Further research to definitively answer the question about the impact of TFAD on mortality, length of stay, readmission or other outcome measures in cellulitis would require significant resources. An adequately-powered randomised controlled trial could control for factors not addressed in the current observational study, such as the level of patient co-morbidity, complexity and antimicrobial appropriateness. However, other identified priorities for cellulitis research [11] suggest that resources may be better utilised investi-

Table 1
Characteristics of the study sample

Characteristic	*n* (%) or median (range); IQR
Demographics ($n = 282$)	
Sex	
Male	181 (64.2)
Female	101 (35.8)
Age at admission (years)	64 (18–97); 48–77
Clinical parameters at presentation ($n = 282$)	
Temperature (°C)	36.6 (34.1–39.9); 36.1–37.2
Heart rate (beats per min)	89 (50–180); 77–102
Respiratory rate (breaths per min)	18 (12–48); 16–20
Systolic blood pressure (mmHg)	130 (65–198); 120–145
WBC count ($\times 10^9$ cells/L) ($n = 271$)	10.2 (1.2–29.9); 7.6–12.5
LOS confounders for cellulitis at presentation[a] ($n = 282$)	
Description	Yes
Obesity	80 (28.4)
Diabetes mellitus	78 (27.7)
Aged >60 years	163 (57.8)
Temperature <36°C or >38°C	84 (29.8)
Heart rate >90 beats per min	123 (43.6)
Respiratory rate >20 breaths per min	40 (14.2)
Elevated or low WBC count (<4 or >12 $\times 10^9$ cells/L) ($n = 273$)	82 (30.0)
Systolic blood pressure <90 mmHg	2 (0.7)
eGFR <45 mL/min ($n = 274$)	48 (17.5%)

IQR, interquartile range; WBC, white blood cell; LOS, length of acute hospital stay; eGFR, estimated glomerular filtration rate.

[a] Adapted from Garg A, Lavian J, Lin G, Sison C, Oppenheim M, Koo B. Clinical characteristics associated with days to discharge among patients admitted with a primary diagnosis of lower limb cellulitis. J Am Acad Dermatol 2017;76:626–31.

gating other management considerations such as initial antimicrobial choice [7].

5. Conclusion

After controlling for confounders, no association between increased TFAD and an increased acute LOS was identified for patients with lower limb cellulitis who did not require ICU admission (i.e. without septic shock). Conclusions could not be made for 30-day readmission rates for cellulitis. Further research to definitively answer the question about the impact of TFAD on mortality, length of stay, readmission or other outcome measures in cellulitis would require an adequately powered randomised controlled trial.

Declaration of Competing Interest

DCMK has sat on advisory boards for Becton Dickinson Pty. Ltd. and MSD and has received financial support from MSD and F2G Ltd. (all unrelated to the current work). All other authors declare no competing interests.

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Ethical approval

This study was approved by the Ballarat Health Services and St John of God Human Research Ethics Committee [LNR/50735/BHSSJOG-2019-172421(v1)].

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