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Prevalence and predictors of initial oral antibiotic treatment failure in adult emergency department patients with cellulitis: a pilot study.

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BMJ Open Prevalence and predictors of initial oral antibiotic treatment failure in adult emergency department patients with cellulitis: a pilot study

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ABSTRACT

Introduction: Assessment of cellulitis severity in the emergency department (ED) setting is problematic. Given the lack of research performed to describe the epidemiology and management of cellulitis, it is unsurprising that heterogeneous antibiotic prescribing and poor adherence to guidelines is common. It has been shown that up to 20.5% of ED patients with cellulitis require either a change in route or dose of the initially prescribed antibiotic regimen. The current treatment failure rate for empirically prescribed oral antibiotic therapy in Irish EDs is unknown. The association of patient risk factors with treatment failure has not been described in our setting. Lower prevalence of community-acquired methicillin-resistant *Staphylococcus aureus*-associated infection, differing antibiotic prescribing preferences and varying availability of outpatient intravenous therapy programmes may result in different rates of empiric antibiotic treatment failure from those previously described.

Methods and analysis: Consecutive ED patients with cellulitis will be enrolled on a 24/7 basis from 3 Irish EDs. A prespecified set of clinical variables will be measured on each patient discharged on empiric oral antibiotic therapy. A second independent study recruiter will assess at least 10% of cases for each of the predictor variables. Follow-up by telephone call will occur at 14 days for all discharged patients where measurement of the primary outcome will occur. Our primary outcome is treatment failure, defined as a change in route of antibiotic administration from oral to intravenous antibiotic. Our secondary outcome is change in dose or type of prescribed antibiotic. A cohort of approximately 152 patients is required to estimate the proportion of patients failing oral antibiotic treatment with a margin of error of 0.05 around the estimate.

Ethics and dissemination: Full ethics approval has been granted. An integrated dissemination plan, involving diverse clinical specialties and enrolled patients, is described.

Trial registration number: NCT 02230813.

INTRODUCTION

Definition and epidemiology of cellulitis

Cellulitis is an infectious process of the dermal and subdermal tissues that is of variable presentation, aetiology and severity.¹ Although necrotising fasciitis and sepsis may develop in a minority, most patients have a low risk of complications.² However, cellulitis and other skin and soft tissue infections (SSTIs) represent a significant disease burden, accounting for between 1.5% and 3% of emergency department (ED) attendances in Britain³ and North America.^{4,5} Cellulitis is a term that is often used interchangeably with erysipelas⁶ and for the purposes of this research proposal, both entities will be considered synonymous with the same disease.

Statement of the problem in the ED setting

Empirically prescribed antibiotic therapy for cellulitis and other SSTIs varies significantly in choice, route and duration of therapy among emergency physicians (EPs)⁴ and hospitalists,¹ who adhere poorly to published guidelines.^{4,7} Furthermore, what guidelines do exist have practically all been derived by expert consensus^{3,8-11} or in cohorts of admitted hospital inpatients. In a recent study of a commonly used guideline in the UK, the Clinical Resource Efficiency Support Team (CREST) guideline,³ it was shown that over 50% of patients suitable for oral antibiotic therapy based on guideline classification were actually prescribed intravenous therapy.⁷ Two other studies have examined the association between predictor variables and failure of empirically prescribed ED antibiotic therapy.^{12,13} Both found that between 18.7% and 20.5% of ED patients prescribed antibiotics subsequently required either admission to hospital, change



from oral to intravenous therapy or change in the type of oral or intravenous antibiotic therapy prescribed. However, both studies were performed in Canada where the prevalence of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA)-associated SSTI is high.^{14–16} Furthermore, they assessed treatment failure in patients receiving intravenous and oral antibiotic therapy in the ED setting, which may not be applicable to settings without developed outpatient intravenous therapy programmes.

The treatment failure rate of initially prescribed oral antibiotic therapy in the ED setting in Ireland is unknown. Furthermore, the association between patient predictor variables and treatment failure has not been described in our setting. The findings of this pilot study will enable us to assess the feasibility of developing a clinical prediction rule (CPR) so that a more evidence-based approach to disposal of ED patients to oral or intravenous antibiotic therapy can be developed. CPRs are clinical tools that quantify the contribution of the patient's history, physical examination and diagnostic tests and assist in the stratification of patients according to the probability of having a target disorder.¹⁷ They are designed to reduce clinical uncertainty in an outcome by assessing the strength of association between the risk of the outcome occurring and baseline characteristics.¹⁸

Objectives

The primary aim of this study is to identify the treatment failure rate of empirically prescribed oral antibiotic therapy for ED patients discharged with cellulitis. Treatment failure is defined as a change in route of antibiotic administration from oral to intravenous antibiotic. Specific objectives are:

1. To pilot a standardised clinical assessment for patients with cellulitis, incorporating variables from medical history, clinical examination and investigation, including a pain numerical rating scale and physician-reported assessment scale;
2. To use this assessment in tandem with current clinical assessment of patients with cellulitis;
3. To determine the treatment failure rate, the loss-to-follow-up rate and the proportion of eligible patients who enrol in the study;
4. To investigate the relationship between patient risk factors and treatment failure;
5. To evaluate reasons why patients are not eligible in order to determine if eligibility criteria need to be changed for the full-scale trial;
6. To assess interobserver reliability.

METHODS AND ANALYSIS

We will conduct a prospective cohort study to enrol ED patients with cellulitis from three hospitals (Beaumont Hospital (BH), Connolly Hospital Blanchardstown and Mater Misericordiae University Hospital (MMUH)) in Dublin, Ireland. The combined annual ED patient attendance volume is approximately 150 000. See online

supplementary material for definitions relevant to study design.

Study population

Consecutive adult patients aged >16 years attending the study EDs with cellulitis will be considered eligible for recruitment to the study. Only those patients deemed suitable for oral antibiotic therapy and planned for discharge will be recruited to the study. Patients will be recruited on a 24/7, round-the-clock basis. Cellulitis may arise de novo, or from a recognised cause such as a wound, abscess or ulcer. In order to generate an externally valid CPR, we will include all patients attending the ED with cellulitis, including those who may have already been started on oral antibiotics.

Inclusion criteria

Patient eligibility will be determined by the treating EP based on the following inclusion criteria:

1. Age >16 years
2. Appearance of typical area of erythema over any body part excluding the perineum, within the preceding 5 days with any two of the following signs:
 - A. Increased warmth over affected area
 - B. Swelling of affected area
 - C. Pain over affected area
3. Regional lymphadenopathy
4. Suitable for treatment with flucloxacillin monotherapy (500 mg–1 g four times daily) or a suitable alternative for penicillin-allergic patients as listed in the local prescribing guidelines.

We will include patients with cellulitis secondary to abscess provided that there is evidence of coexisting cellulitis. Standard therapy for abscess is permitted including incision and drainage, irrigation and packing.

Exclusion criteria

Respondents meeting any of the following criteria will be excluded from the study:

1. Clinical requirement for intravenous antibiotics as decided by the treating clinician;
2. Age less than 16 years;
3. No telephone or access to a telephone;
4. Abscess alone without coexisting signs of cellulitis;
5. Mammalian bite wounds;
6. Infected diabetic foot ulcer;
7. Necrotising soft tissue infections;
8. Perineal cellulitis (increased risk of Fournier's gangrene);
9. Suspected septic arthritis or osteomyelitis;
10. Decubitus ulcers;
11. Bilateral cellulitis (as this entity rarely exists);
12. Acute lipodermatosclerosis;
13. Acute dermatitis;
14. Venous stasis dermatitis;
15. Deep vein thrombosis;
16. Pregnancy;
17. Cognitive impairment;

18. Any patient who through language barrier or diminished capacity is unable to understand the scope of the study.

Patient assessment

Patients will be recruited by EPs and advanced nurse practitioners (ANPs) in emergency medicine (EM), both of whom are required to have at least 2 years post-graduate experience in EM. We will explicitly advise treating EPs or ANPs ('first study recruiters') not to alter their patient care for this study, but to continue with usual care. Suitable patients meeting the prespecified inclusion criteria will be invited to participate in the study by the first study recruiter. An information leaflet will be given to them to read. A verbal explanation of the study aims and procedure will also be conveyed. After allowing the patient time to read the study patient information leaflet (PIL), informed written consent will be obtained from the patient.

Consenting patients will be given a study questionnaire to complete. All study co-investigators and two laypersons reviewed this questionnaire for ease of reading. The first study recruiter will complete the listed predictor variables in a standardised, closed-response case report form (CRF) by interview and examination of the patient (see online supplementary material). Definitions for each of the predictor variables will be made available with the CRF. Any queries that may arise during completion of the questionnaire will be addressed at this time.

When feasible, a second EP or ANP ('second study recruiter'), blinded to the first study recruiter's assessment will examine the patient and record the presence of predictor variables. After assessment, the second study recruiter will give their opinion as to whether they would recommend oral or intravenous antibiotic therapy for the patient. The second study recruiter must also have at least 2 years postgraduate experience in EM and will be asked to remain independent of the first recruiter's patient assessment and final decision for oral antibiotic therapy. At least 10% of all patient assessments will be completed by a second study recruiter.

In order to ensure standardised data collection all enrolling EPs and ANPs will be provided with a 30 min individual training session regarding the study procedures. Paper CRFs will be completed at the patient bedside separately to their medical notes. ED clinical records will also be completed in the standard fashion.

General practitioner (GP) contact details will be recorded at the time of consent and patients will be asked to permit the investigators to discuss their clinical course with their GP and to access their healthcare records in order to complete the case report form.

Quality assurance

Throughout the duration of the study, the completeness of data collection and compliance with patient enrolment will be quality assured. Follow-up of missed enrolments will be achieved by cross-referencing ED

discharged patients with cellulitis from each participating ED's patient database. Study recruiters will be given regular feedback regarding the quality and completeness of their data collection.

Selection of variables

The variables selected for assessment in the study were chosen based on two observational studies,^{19 20} a literature review and input from all study investigators. The number of variables collected was limited to ensure efficient completion of the data forms in the context of usual patient care by study recruiters. The variables to be collected are summarised in [box 1](#).

Patient allocation

Patients will be discharged on a 7–14 day course of an oral antibiotic recommended by the local hospital prescribing guideline, which in the case of patients not

Box 1 Patient predictor variables

History

Age (years)*

Gender (male/female)*

Self-referral (yes/no)*

Pre-emergency department antibiotic therapy duration (in days)*

Level of pain in affected area (validated numerical scale)*

Rigors or self-reported fever*

Medical history

Chronic underlying comorbidity (eg, chronic kidney or liver disease, chronic heart failure)

Body mass index calculated by weight/height²*

Previous episode of cellulitis in same area (yes/no)*

Peripheral vascular disease

Previous surgery to affected area*

Venous insufficiency (1 of leg ulcer, venous eczema, phlebitis)

Diabetes mellitus (yes/no)

Social history

Smoking (yes/no)*

Intravenous drug use (yes/no)

Heart rate (bpm)

Temperature (°C)

Systolic blood pressure (mm/Hg)

Respiratory rate (breaths/min)

Oxygen saturation on room air (%)

Level of awareness (Alert, Voice, Pain, Unresponsive (AVPU scale))

Capillary blood glucose (mmol/L)

C reactive protein (mmol/L)

White cell count (mmol/L)

Local clinical variables

Maximum diameter of infection (cm)

Ulcer (yes/no)

Wound (surgical or traumatic) (yes/no)

Athletes' foot (interdigital skin breakdown/exudate in >1 web space) (yes/no)

Fungal nail infection in affected leg if applicable

Skin breakdown due to underlying skin condition

Chronic limb oedema, including lymphoedema in affected limb (yes/no)

*Assessed on patient questionnaire.



allergic to penicillin in the participating EDs, is flucloxacillin 500 mg–1 g four times a day. Patients allergic to penicillin will be treated according to local hospital prescribing policy, which in each of the study sites recommends either doxycycline, clindamycin or erythromycin. Currently, the standard treatment is to discharge the patient to the care of their GP. Patients enrolled will be specifically asked to return to the treating ED for review if their symptoms deteriorate while on oral antibiotic treatment.

Patient follow-up

All patients will be consented for follow-up by telephone contact at 14 days after the initial ED visit.

At this telephone review patients will be asked:

1. Whether their symptoms improved with oral antibiotic treatment;
2. Whether they re-presented to a healthcare setting for a change in antibiotic drug, dose or route of administration;
3. How they have felt since their last visit, with a description of any adverse events;
4. Whether they have had to change their antibiotic due to side effects such as diarrhoea, nausea, vomiting or thrush;
5. Whether they wish to receive the final study results.

For patients who are not contactable by telephone at day 14, consent will be obtained for their GP to be contacted instead. Their GP will be asked whether the patient has attended for review or to a hospital within the previous 14 days with symptoms of cellulitis. Patients will be described as a ‘treatment response’ if their symptoms have improved and ‘treatment failure’ if they have required a change from oral to intravenous antibiotic therapy. If at telephone interview the patient describes worsening infection but has not yet attended a healthcare setting for review, he/she will be advised to attend their treating ED and recorded as a treatment failure. We will also record our secondary outcomes at telephone interview (change in prescribed oral antibiotics to a different oral antibiotic, increased dose of prescribed oral antibiotic).

Outcome measures

The primary outcome is treatment failure defined as a change in route of antibiotic administration from oral antibiotic to intravenous antibiotic.

Secondary outcome measures are:

1. Treatment failure measured by change in prescribed oral antibiotic to another oral antibiotic.
2. Treatment failure measured by the change in prescribed dose of oral antibiotic to a higher dose of the same antibiotic.
3. Assessment of interobserver reliability for the clinical variables listed in box 1. This will be performed in at least 10% of patients enrolled into the study by a second recruiting clinician.
4. Assessment of the eligibility and loss-to-follow-up rate.

Data analysis

Assessment of treatment failure

For measurement of the primary outcome (treatment failure rate), the number of patients who fail oral antibiotic treatment will be expressed as a percentage of the total number of patients prescribed oral antibiotic treatment. For the secondary outcome (change in dose or type of prescribed antibiotic), the percentage of patients whose oral antibiotic prescribed in the ED is changed to another oral antibiotic, or whose dose of oral antibiotic is changed to a higher dose of the same antibiotic, will be calculated.

Univariate associations between the explanatory variables and treatment failure will also be examined. These results will be expressed as ORs; values of >1 indicating increased odds of failing oral antibiotic treatment and values of <1 indicating decreased odds of failing oral antibiotic treatment. Explanatory variables considered of prior clinical importance or having a threshold p value of ≤ 0.15 in the univariate analysis will be included in a multivariable logistic regression model.

Interobserver agreement

At least 10% of all patient assessments will be completed by a second study recruiter. The interobserver agreement for each variable listed in table 1 will be assessed by calculating the κ coefficient along with 95% CIs. For variables with three or more ordered categories a weighted κ will be calculated. A variable will be deemed to have an acceptable agreement if the κ coefficient has a value of at least 0.6.²¹

Feasibility

Feasibility will be assessed in terms of recruitment, response rates, loss to follow-up and eligibility.

Sample size

The sample size of this pilot study has been estimated based on determining the proportion of patients failing oral antibiotic treatment. Using a 95% CI for the proportion of patients failing oral antibiotic treatment, a margin of error of 0.05 and an expected proportion of 10% based on an educated guess, and two recent studies^{15 16} suggesting that at least 6.8%, and up to 20% of ED patients with cellulitis fail initially prescribed antibiotic therapy, the required sample for the pilot study would be at least 152 patients.

ETHICAL ISSUES AND DISSEMINATION PLAN

The study protocol has received Research and Ethics Committee approval from each recruiting site for initiation. In order to prevent the likelihood of an adverse event such as the enrolment of a patient with sepsis, we have not permitted junior doctors with less than 2 years postgraduate experience in medicine or surgery to recruit patients. We would hope that having a senior staff member

see each patient prior to discharge should reduce the risk of such an occurrence from happening.

Adverse events will be specifically enquired for at the telephone interview. Although not an ideal medium for patient assessment it will provide a method to address patient concerns and provide advice. Patients will be advised to attend the referring ED for review if there are concerns. Patients will also be asked if they would like to directly receive, via mail or email, the final study results as a lay summary and/or as the finally published manuscript.

Although this is a pilot study, we aim to use the findings of this study to inform a larger CPR derivation project. As such, integrated knowledge management with EPs, ANPs and patients will be crucial to the long-term success of the study. We will present our findings at national and international conferences and publish our research findings in a reputable peer-reviewed journal. Our research is of considerable relevance to primary care, which directs a large proportion of cellulitis treatment in the Irish community. To address this, we will supply each referring GP with a letter informing them of the inclusion of their patient in this study, and disseminate our study results by publication in suitable primary care literature and through regular educational meetings. Our research study group is a collaboration between the main specialties that manage cellulitis in Ireland, namely primary care, EM and general surgery.

Limitations

The three study sites serve a population where the endemic rate of CA-MRSA is low. As a result, the findings may not be generalisable to all settings. Since telephone follow-up will be used, patient recall bias may be introduced to the study. However, since telephone follow-up of patients with skin infections has been previously used in a similar research study,¹³ and patients with deteriorating symptoms will be instructed to re-present to an ED for assessment, we believe this method of patient follow-up is feasible.

DISCUSSION

The proposed study aims to identify the treatment failure rate of empirically prescribed oral antibiotic therapy for cellulitis in three Irish EDs. We will also examine the association between patient risk factors for cellulitis and treatment failure. The findings of this pilot study will permit this research group to assess sample size, and feasibility, for a future, larger CPR derivation project.

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Contributors MQ and AW conceived of the study and drafted the manuscript. TF and ROS contributed to study design and methodology and helped draft the manuscript. FB contributed to study design and statistical methodology. IS and AH provided advice regarding study methodology.

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