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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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TITLE PAGE

Title:

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

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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 recently shown that up to 20.5% of all cases of cellulitis treated on an outpatient basis with empiric oral or IV antibiotics require either a change in route or dose of the initially prescribed regimen.

The current treatment failure rate for empirically prescribed oral antibiotic therapy in Irish EDs is unknown. Furthermore, 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 IV 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 2 Irish EDs. A pre-specified 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 IV 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.

Registration

This study was registered with ClinicalTrials.gov (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 necrotizing 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 (SSTI) represent a significant disease burden, accounting for between 1.5% - 3% of Emergency Department (ED) attendances in Britain [3] and North America [4, 5]. Cellulitis is a term that is often used interchangeably with erysipelas [6] 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 (IV) therapy [7]. There are only 2 other studies that have examined the association between patient 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 IV therapy or change in the type of oral or IV antibiotic therapy prescribed. However, both were performed in Canada where the prevalence of community-acquired methicillin-resistant *Staphylococcus aureus* (CAMRSA)-associated SSTI is high [14-16]. Furthermore, they assessed treatment failure in patients receiving IV and oral antibiotic therapy in the ED setting, which may not be applicable to settings without developed outpatient IV therapy programmes.

The treatment failure rate of initially prescribed oral antibiotic therapy in the ED setting in Ireland in 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 IV antibiotic therapy can be developed. CPRs are clinical tools that quantify the contribution of the history, physical examination and diagnostic tests and assist in the stratification of patients according to the probability of having a target disorder. 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 [17].

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 antibiotic to IV 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 inter-observer reliability.

METHODS AND ANALYSIS

We will conduct a prospective cohort study to enrol ED patients with cellulitis from two hospitals (Beaumont Hospital (BH) and Mater Misericordiae University Hospital (MMUH)) in Dublin, Ireland. The combined annual ED patient

attendance volume is approximately 110,000. See supplemental file 1 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 commenced on oral antibiotics.

Inclusion criteria

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

I. Age >16 years

II. Appearance of typical area of erythema over any body part excluding the perineum, within the preceding 5 days with any 2 of the following signs:

1. Increased warmth over affected area
2. Swelling of affected area
3. Pain over affected area
4. Regional lymphadenopathy

III. Suitable for treatment with flucloxacillin monotherapy (500 mg -1 gram qds) 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 co-existing cellulitis. Standard therapy for abscess is permitted including incision and drainage, irrigation and packing.

Exclusion criteria

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

i. Clinical requirement for IV antibiotics as decided by the treating clinician.
ii. Age less than 16 years.
iii. No telephone or access to a telephone.
iv. Abscess alone without co-existing signs of cellulitis
v. Mammalian bite wounds.
vi. Infected diabetic foot ulcer
vii. Necrotising soft tissue infections.
viii. Perineal cellulitis (increased risk of Fournier's gangrene).
ix. Suspected septic arthritis or osteomyelitis.
x. Decubitus ulcers.
xi. Bilateral cellulitis (as this entity rarely exists).
xii. Acute lipodermatosclerosis.
xiii. Acute dermatitis.
xiv. Venous stasis dermatitis.
xv. Deep vein thrombosis.

xvi. Pregnancy.

xvii. Cognitive impairment.

xviii. 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 postgraduate 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 pre-specified 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. This questionnaire has been reviewed by all study co-investigators and 2 lay persons 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 (supplementary file 1). Each of the predictor variables are defined in supplemental file 2 and 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 IV 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-minute, 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 [20, 21], 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 Table 1.

Table 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 *
Past Medical History
Chronic underlying co-morbidity (e.g. chronic kidney or liver disease, chronic heart failure)

BMI calculated by weight / height ^{2} *
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 (beats per minute)
Temperature (degrees Celsius)
Systolic blood pressure (mm/Hg)
Respiratory rate (breaths per minute)
Oxygen saturation on room air (%)
Level of awareness (Alert, Voice, Pain, Unresponsive Scale [AVPU])
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

Patient allocation

Patients will be discharged on a 7-to-14 day course of an oral antibiotic recommended by the local hospital prescribing guideline, which in the case of patients not allergic to penicillin in the participating EDs, is flucloxacillin 500 mg – 1 gram four times daily. 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 (day 14).

At this telephone review patients will be asked:

I. Whether their symptoms improved with oral antibiotic treatment.

II. Whether they re-presented to a healthcare setting for a change in antibiotic drug, dose or route of administration.

III. How they have felt since their last visit, with a description of any adverse events.

IV. Whether they have had to change their antibiotic due to side effects such as diarrhoea, nausea, vomiting or thrush.

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 IV antibiotic therapy. If at telephone interview the patient describes worsening infection but has not yet attended a health care 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 (IV) 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 inter-observer reliability for the clinical variables listed in Table 2. 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 the primary outcome (the oral antibiotic treatment failure rate), the number of patients who fail oral antibiotic therapy prescribed in the ED will be expressed as a percentage of the total number of patients who are prescribed therapy. 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 (table 2) and treatment failure will also be examined. These results will be expressed as odd ratios (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 have a threshold p-value of ≤ 0.15 in the univariate analysis will be included in a multivariable logistic regression model.

Inter-observer agreement

At least 10% of all patient assessments will be completed by a second study recruiter. The inter-observer agreement for each variable listed in Table 2 will be assessed by calculating the kappa coefficient along with 95% confidence

intervals. For variables with three or more ordered categories a weighted kappa will be calculated. A variable will be deemed to have an acceptable agreement if the kappa coefficient has a value of at least 0.6 [18].

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% confidence interval (CI) for the proportion of patients failing oral antibiotic treatment, a margin of error (ME) 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 cellulitis patients 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 Beaumont Hospital Research and Ethics Committee approval for commencement. 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.

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 specialities that manage cellulitis in Ireland, namely primary care, emergency medicine and general surgery.

DISCUSSION

The proposed study aims to identify the treatment failure rate of empirically prescribed oral antibiotic therapy for cellulitis in two 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 CPR derivation project.

Abbreviations

ED: Emergency Department

SSTI: Skin and Soft Tissue Infection

CRF: Case Report Form

OR: Odds Ratio

IV: Intravenous

CPR: Clinical Prediction Rule

GP: General Practitioner

ANP: Advanced Nurse Practitioner

Authors contributions

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.

Funding statement

There is currently no funding for this study.

Competing Interests

None.

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CASE REPORT FORM

Page 2 and 3:	To be completed by first study recruiter
Page 4.	To be completed by patient
Page 5.	To be completed by second study recruiter *
Page 6:	To be completed by Principal Investigator / Co-Investigator

- **10% of all study forms must be completed by a second study recruiter.**
- The second study recruiter must fulfill the following criteria:
    1. Be independent and blinded to the first recruiter's case report form.
    2. Be blinded to the final decision to prescribe oral or IV antibiotics for the patient.

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First Study Recruiter

Please complete the following in addition to your ED clinical records and assist the patient with the questionnaire as needed.

Date: __/___/_____

Time: _____

Consent obtained? **Yes☐ No ☐**

If no, what is the reason for not enrolling the patient?
Refused consent?
No telephone?
Social reasons (e.g. homeless)?

_____
_____

Patient enrolment ID number: _____

Was the patient taking oral antibiotics prior to ED attendance? _____**Yes ☐No ☐**

If yes, Name _____ Dose _____ Duration _____ *in days*

Temp __.__ °C	Capillary blood glucose (if done)_____mmol/L
HR _____ / min	CRP (if done) _____mmol/L
BP ___ / ___ mmHg	WCC (if done)_____mmol/L
RR __ / min	
SpO_2 __ %	
Level of awareness: Alert☐ Voice☐ Pain☐ Unresponsive☐	

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First Study Recruiter

Location of infection _____

Lesion size:

Length ("aligned head to toe") _____cm Width ("maximum diameter")_____

	Yes	No
Purulent discharge	☐	☐
Erythema	☐	☐
Fluctuance	☐	☐
Oedema	☐	☐
Pain	☐	☐
Lymphangitis	☐	☐
Ulcer	☐	☐
Wound (surgical or traumatic) Please specify _____	☐	☐
Athletes' Foot (Interdigital skin breakdown/exudate in >1 web space)	☐	☐
Fungal nail infection in affected leg (if applicable)	☐	☐
Skin breakdown due to underlying skin condition	☐	☐
Chronic limb oedema (including lymphoedema)	☐	☐
Medical History		
Chronic underlying co-morbidity (chronic kidney/liver/cardiac disease)	☐	☐
Peripheral Vascular Disease	☐	☐
Venous Insufficiency (1 of leg ulcer, venous eczema, phlebitis)	☐	☐
Diabetes mellitus (either Type 1 or 2)	☐	☐
Intravenous Drug Use	☐	☐

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Patient Questionnaire:

Please complete the following questionnaire to the best of your ability. Details about this study will have been given to you in the information leaflet. If you have any queries regarding the questions asked, please ask for help from the doctor or nurse treating you.

Your phone no.: Mobile _____Landline_____

Next-of-kin phone no.: Mobile _____ Landline_____

GP name: _____

Age: _____ years

Gender: Female ☐ Male ☐

Are you a smoker: **Yes ☐No ☐**

Your weight: _____
(circle: kg or stones or lb)

Your height: _____
(circle: ft or cm)

What part of your body is affected by this infection?_____

In the past year, have you had a similar infection in the same part of your body as now?
_____ **Yes ☐ No ☐**

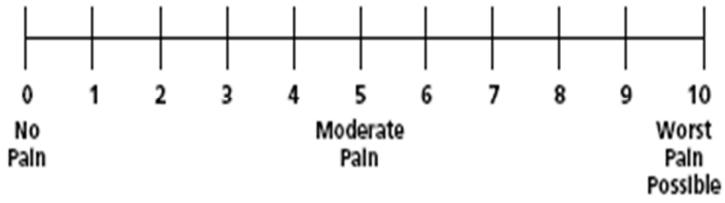
Have you ever had surgery, of any kind, to the same part of your body that is now infected?_____ **Yes ☐No ☐**

Were you referred by your GP? _____ **Yes ☐No ☐**

Did you notice any uncontrolled shivering of your body? _____**Yes ☐No ☐**

Did you have a fever at home prior to coming to hospital?_____ **Yes ☐No ☐**

Choose a number from 0 to 10 that best describes your current pain.
"0" would mean 'No pain' and 10 would mean 'Worst possible pain'.
Mark the chart below at the number that best describes your current pain.



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Second Study Recruiter

Please examine the patient and complete the following variables

Location of infection _____

Maximum measured diameter of area of erythema _____cms

	Yes	No
Ulcer	☐	☐
Wound (surgical or traumatic) Please specify _____	☐	☐
Athletes' Foot (Interdigital skin breakdown/exudate in >1 web space)	☐	☐
Fungal nail infection in affected leg (if applicable)	☐	☐
Skin breakdown due to underlying skin condition	☐	☐
Chronic limb oedema (including lymphoedema)	☐	☐
Medical History		
Chronic underlying co-morbidity (chronic kidney/liver/cardiac disease)	☐	☐
Peripheral Vascular Disease	☐	☐
Venous Insufficiency (1 of leg ulcer, venous eczema, phlebitis)	☐	☐
Diabetes mellitus (either Type 1 or 2)	☐	☐
Intravenous Drug Use	☐	☐

In your opinion, what is the most likely diagnosis?_____

In your opinion, will cure be achieved with oral antibiotics? **Yes** ☐ **No** ☐

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Telephone follow-up

Day post enrolment: Day_____

Regarding the infection for which you were treated with antibiotics, has there been a decrease in the size of the area of infection by at least 50% from when you were first treated?

Increase ☐ **Decrease** ☐

Do you believe your infection has been cured?

Yes ☐ **No** ☐

Have you received antibiotic injections directly into a vein (intravenously) for your infection since your first assessment?

Yes ☐ **No** ☐

Have you required a second course of antibiotic tablets from your GP or from another doctor since you were first treated in the Emergency Department with this infection?

Yes ☐ **No** ☐

How have you felt since your first visit?

Well ☐ ***Unwell*** ☐

(Any adverse events should be recorded at this point in time. Describe in detail any untoward (unexpected or inappropriate) medical event regardless of its causal relationship to study treatment.)

Adverse event description _____
*Date of onset*_____
Duration _____
Resolution _____
*Severity*_____
*Outcome (Recovery, continuing, worsening, death)*_____
Relationship to treatment for cellulitis?
*Unrelated/Possible/Probable/Definite*_____

Did you require a change in your antibiotic prescription due to a skin rash or other side effect (such as diarrhoea, nausea, vomiting, thrush)?
*Please specify*_____
_____
_____

Supplemental file 2

Definitions relevant to study design.

Treatment failure:

(i) no change or increase in the maximal diameter of the area of infection despite treatment as reported by patient (primary outcome)

(ii) change from oral to IV antibiotic at any time point within 2 weeks of enrolment (primary outcome)

(iii) increase in dose of prescribed oral treatment (secondary outcome)

(iv) change in prescribed oral treatment (secondary outcome)

Treatment response:

self-reported improvement in size of area of cellulitis and reduction in symptoms.

Venous Ulcer: area of epithelial defect present due to underlying venous disease

Abscess: Accumulation of pus within the skin or subcutaneous tissues.

(Requires co-exisintg cellulitis for inclusion to the study)

Mammalian bite wound: any human or animal bite that breaches the dermis

Venous insufficiency: at least one of a history of leg ulcer, leg phlebitis or venous dermatitis.

Chronic limb oedema: pitting oedema greater than grade + that is due to primary or secondary lymphatic obstruction (lymphedema), chronic congestive cardiac failure, chronic venous insufficiency or drug side effects.

Interdigital maceration ("athletes foot"): skin breakdown and/or exudate from the interdigital cleft of the foot due to tinea pedis infection.

Intravenous drug use: self-reported illicit drug injection.

Height: patient reported height in feet/inches or in metre/centimetres.

Weight: patient reported weight in stones or pounds or kilograms

Upper extremity: from shoulder to wrist.

Lower extremity: from inguinal ligament to the distal toes.

Hand: from the wrist to the distal fingers.

Chest: from the sternoclavicular joint to the tip of the xiphoid process.

Abdomen: from the xiphoid process to the pubic symphysis.

Back: from C7 to the natal cleft.

Perineum: bounded by the thighs laterally and the symphysis superiorly and the natal cleft.

Face: angle of mandible to vertex of skull.

Postoperative infections: any infection occurring at the site of a surgical procedure within previous 3 months

Previous antibiotic use: any antibiotic use for any cause within 7 days.

Diabetic foot ulcer: Ulcer arising in a person with diabetes due to underlying neurovascular impairment.

Self –referral: Arrival to the ED by any means without referral by another physician

Peripheral vascular disease: history of known peripheral arterial insufficiency, history of vascular surgery, or presumed arterial insufficiency due to clinical findings.

Diabetes mellitus: type I or type II indicated by self-report, medical history, electronic medical record, use of hypoglycemic oral agents, insulin administration, or blood glucose >11.1mmol/L

Previous surgery to the affected area: Any previous surgical procedure in the affected area.

Ulcer: epithelial defect due to venous or arterial insufficiency

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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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TITLE PAGE

Title:

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 IV 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 pre-specified 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 IV 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 specialities and enrolled patients, is described.

Registration

ClinicalTrials.gov (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 necrotizing 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 (SSTI) represent a significant disease burden, accounting for between 1.5% - 3% of Emergency Department (ED) attendances in Britain [3] and North America [4, 5]. Cellulitis is a term that is often used interchangeably with erysipelas [6] 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 (IV) therapy [7]. There are only 2 other studies that have examined the association between patient 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 IV therapy or change in the type of oral or IV antibiotic therapy prescribed. However, both were performed in Canada where the prevalence of community-acquired methicillin-resistant *Staphylococcus aureus* (CAMRSA)-associated SSTI is high [14-16]. Furthermore, they assessed treatment failure in patients receiving IV and oral antibiotic therapy in the ED setting, which may not be applicable to settings without developed outpatient IV therapy programmes.

The treatment failure rate of initially prescribed oral antibiotic therapy in the ED setting in Ireland in 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 IV antibiotic therapy can be developed. CPRs are clinical tools that quantify the contribution of the 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 antibiotic to IV 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 inter-observer 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 supplemental file 1 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 commenced on oral antibiotics.

Inclusion criteria

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

I. Age >16 years

II. Appearance of typical area of erythema over any body part excluding the perineum, within the preceding 5 days with any 2 of the following signs:

    1. Increased warmth over affected area
    2. Swelling of affected area
    3. Pain over affected area
    4. Regional lymphadenopathy

III. Suitable for treatment with flucloxacillin monotherapy (500 mg -1 gram qds) 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 co-existing cellulitis. Standard therapy for abscess is permitted including incision and drainage, irrigation and packing.

Exclusion criteria

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

i. Clinical requirement for IV antibiotics as decided by the treating clinician.
ii. Age less than 16 years.
iii. No telephone or access to a telephone.
iv. Abscess alone without co-existing signs of cellulitis
v. Mammalian bite wounds.
vi. Infected diabetic foot ulcer
vii. Necrotising soft tissue infections.
viii. Perineal cellulitis (increased risk of Fournier's gangrene).
ix. Suspected septic arthritis or osteomyelitis.
x. Decubitus ulcers.
xi. Bilateral cellulitis (as this entity rarely exists).
xii. Acute lipodermatosclerosis.
xiii. Acute dermatitis.
xiv. Venous stasis dermatitis.
xv. Deep vein thrombosis.
xvi. Pregnancy.
xvii. Cognitive impairment.

xviii. 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 postgraduate 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 pre-specified 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 lay-persons 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 (supplementary file 1). Each of the predictor variables are defined in supplemental file 2 and 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 IV 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-minute, 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 Table 1.

Patient allocation

Patients will be discharged on a 7-to-14 day course of an oral antibiotic recommended by the local hospital prescribing guideline, which in the case of patients not allergic to penicillin in the participating EDs, is flucloxacillin 500 mg – 1 gram four times daily. 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 (day 14).

At this telephone review patients will be asked:

I. Whether their symptoms improved with oral antibiotic treatment.

II. Whether they re-presented to a healthcare setting for a change in antibiotic drug, dose or route of administration.

III. How they have felt since their last visit, with a description of any adverse events.

IV. Whether they have had to change their antibiotic due to side effects such as diarrhoea, nausea, vomiting or thrush.

V. 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 IV antibiotic therapy. If at telephone interview the patient describes worsening infection but has not yet attended a health care 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 (IV) 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 inter-observer reliability for the clinical variables listed in Table 2. 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 the primary outcome (the oral antibiotic treatment failure rate), the number of patients who fail oral antibiotic therapy prescribed in the ED will be expressed as a percentage of the total number of patients who are prescribed therapy. 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 (table 2) and treatment failure will also be examined. These results will be expressed as odd ratios (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 have a threshold p-value of ≤ 0.15 in the univariate analysis will be included in a multivariable logistic regression model.

Inter-observer agreement

At least 10% of all patient assessments will be completed by a second study recruiter. The inter-observer agreement for each variable listed in Table 2 will be assessed by calculating the kappa coefficient along with 95% confidence intervals. For variables with three or more ordered categories a weighted kappa will be calculated. A variable will be deemed to have an acceptable agreement if the kappa 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% confidence interval (CI) for the proportion of patients failing oral antibiotic treatment, a

margin of error (ME) 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 cellulitis patients 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 commencement. 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 specialities that manage cellulitis in Ireland, namely primary care, emergency medicine 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.

Abbreviations

ED: Emergency Department

SSTI: Skin and Soft Tissue Infection

CRF: Case Report Form

OR: Odds Ratio

IV: Intravenous

CPR: Clinical Prediction Rule

GP: General Practitioner

ANP: Advanced Nurse Practitioner

Authors contributions

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.

Competing interests

None.

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TABLES

Table 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 *
Past Medical History
Chronic underlying co-morbidity (e.g. chronic kidney or liver disease, chronic heart failure)
BMI calculated by weight / height ^{2} *
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 (beats per minute)

Temperature (degrees Celsius)
Systolic blood pressure (mm/Hg)
Respiratory rate (breaths per minute)
Oxygen saturation on room air (%)
Level of awareness (Alert, Voice, Pain, Unresponsive Scale [AVPU])
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

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

CASE REPORT FORM

Page 2 and 3:	To be completed by first study recruiter
Page 4.	To be completed by patient
Page 5.	To be completed by second study recruiter *
Page 6:	To be completed by Principal Investigator / Co-Investigator

- **10% of all study forms must be completed by a second study recruiter.**
- The second study recruiter must fulfill the following criteria:
    1. Be independent and blinded to the first recruiter's case report form.
    2. Be blinded to the final decision to prescribe oral or IV antibiotics for the patient.

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

First Study Recruiter

Please complete the following in addition to your ED clinical records and assist the patient with the questionnaire as needed.

Date: __/___/_____

Time: _____

Consent obtained? **Yes☐ No ☐**

If no, what is the reason for not enrolling the patient?
Refused consent?
No telephone?
Social reasons (e.g. homeless)?

_____
_____

Patient enrolment ID number: _____

Was the patient taking oral antibiotics prior to ED attendance? _____**Yes ☐No ☐**

If yes, Name _____ Dose _____ Duration _____ *in days*

Temp __ __. __ °C	Capillary blood glucose (if done)_____mmol/L
HR _____ / min	CRP (if done) _____mmol/L
BP __ __ __ / __ __ __ mmHg	WCC (if done)_____mmol/L
RR __ __ / min	
SpO_2 __ __ %	
Level of awareness: Alert☐ Voice☐ Pain☐ Unresponsive☐	

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

First Study Recruiter

Patient enrolment ID number: _____

Location of infection _____

Lesion size:

Length ("aligned head to toe") _____cm Width ("maximum diameter")_____

	Yes	No
Purulent discharge	☐	☐
Fluctuance from abscess	☐	☐
Lymphangitis	☐	☐
Ulcer	☐	☐
Wound (surgical or traumatic) Please specify _____	☐	☐
Athletes' Foot (Interdigital skin breakdown/exudate in >1 web space)	☐	☐
Fungal nail infection in affected leg (if applicable)	☐	☐
Skin breakdown due to underlying skin condition	☐	☐
Chronic limb oedema (including lymphoedema)	☐	☐
Medical History		
Chronic underlying co-morbidity (chronic kidney/liver/cardiac disease)	☐	☐
Peripheral Vascular Disease	☐	☐
Venous Insufficiency (1 of leg ulcer, venous eczema, phlebitis)	☐	☐
Diabetes mellitus (either Type 1 or 2)	☐	☐
Intravenous Drug Use	☐	☐

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

Patient Questionnaire:

Please complete the following questionnaire to the best of your ability. Details about this study will have been given to you in the information leaflet. If you have any queries regarding the questions asked, please ask for help from the doctor or nurse treating you.

Your phone no.: Mobile _____Landline_____

Next-of-kin phone no.: Mobile _____ Landline_____

GP name: _____

Age: _____ years

Gender: Female ☐ Male ☐

Are you a smoker: **Yes ☐No ☐**

Your weight: _____
(circle: kg or stones or lb)

Your height: _____
(circle: ft or cm)

What part of your body is affected by this infection?_____

In the past year, have you had a similar infection in the same part of your body as now?
_____ **Yes ☐ No ☐**

Have you ever had surgery, of any kind, to the same part of your body that is now infected?_____ **Yes ☐No ☐**

Were you referred by your GP? _____ **Yes ☐No ☐**

Did you notice any uncontrolled shivering of your body? _____**Yes ☐No ☐**

Did you have a fever at home prior to coming to hospital?_____ **Yes ☐No ☐**

Choose a number from 0 to 10 that best describes your current pain.
"0" would mean 'No pain' and 10 would mean 'Worst possible pain'.
Mark the chart below at the number that best describes your current pain.

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Second Study Recruiter

Please examine the patient and complete the following variables

Patient enrolment ID number: _____

Location of infection _____

Length ("aligned head to toe") _____cm Width ("max diameter")_____

	Yes	No
Purulent discharge	☐	☐
Fluctuance from abscess	☐	☐
Lymphangitis	☐	☐
Ulcer	☐	☐
Wound (surgical or traumatic) Please specify _____	☐	☐
Athletes' Foot (Interdigital skin breakdown/exudate in >1 web space)	☐	☐
Fungal nail infection in affected leg (if applicable)	☐	☐
Skin breakdown due to underlying skin condition	☐	☐
Chronic limb oedema (including lymphoedema)	☐	☐

Medical History

Chronic underlying co-morbidity (chronic kidney/liver/cardiac disease)	☐	☐
Peripheral Vascular Disease	☐	☐
Venous Insufficiency (1 of leg ulcer, venous eczema, phlebitis)	☐	☐
Diabetes mellitus (either Type 1 or 2)	☐	☐
Intravenous Drug Use	☐	☐

In your opinion, what is the most likely diagnosis?_____

In your opinion, will cure be achieved with oral antibiotics? **Yes** ☐ **No** ☐

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Telephone follow-up

Day post enrolment: Day_____

Regarding the infection for which you were treated with antibiotics, has there been a decrease in the size of the area of infection by at least 50% from when you were first treated?

Increase ☐ **Decrease** ☐

Do you believe your infection has been cured?

Yes ☐ **No** ☐

Have you received antibiotic injections directly into a vein (intravenously) for your infection since your first assessment?

Yes ☐ **No** ☐

Have you required a second course of antibiotic tablets from your GP or from another doctor since you were first treated in the Emergency Department with this infection?

Yes ☐ **No** ☐

How have you felt since your first visit?

Well ☐ ***Unwell*** ☐

(Any adverse events should be recorded at this point in time. Describe in detail any untoward (unexpected or inappropriate) medical event regardless of its causal relationship to study treatment.)

Adverse event description _____
*Date of onset*_____
Duration _____
Resolution _____
*Severity*_____
*Outcome (Recovery, continuing, worsening, death)*_____
Relationship to treatment for cellulitis?
*Unrelated/Possible/Probable/Definite*_____

Did you require a change in your antibiotic prescription due to a skin rash or other side effect (such as diarrhoea, nausea, vomiting, thrush)?
*Please specify*_____
_____
_____

Does the patient wish to receive the final study results?
Yes ☐ **No** ☐

If yes, specify lay summary, full manuscript or both _____