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## **A Pilot Cross-Sectional Study of Patients Presenting with Cellulitis to Emergency Departments**

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### **Abstract**

To characterise the Emergency Department (ED) prevalence of cellulitis, factors predicting oral antibiotic therapy and the utility of the Clinical Resource Efficiency Support Team (CREST) guideline in predicting patient management in the ED setting, a prospective, cross-sectional study of consecutive adult patients presenting to 3 Irish EDs was performed. The overall prevalence of cellulitis was 12 per 1,000 ED visits. Of 59 patients enrolled, 45.8% were discharged. Predictors of treatment with oral antibiotics were: CREST Class 1 allocation (odds ratio (OR) 6.81, 95% CI = 1.5-30.1,  $p=0.012$ ), patient self-referral (OR= 6.2, 95% CI 1.9 – 20.0,  $p=0.03$ ) and symptom duration longer than 48 hours (OR 1.2, 95% CI = 1.0-1.5,  $p=0.049$ ). In conflict with guideline recommendation, 43% of patients in CREST Class 1 received IV therapy. Treatment with oral antibiotics was predicted by CREST Class 1 allocation, self-referral, symptom duration of more than 48 hours and absence of pre-ED antibiotic therapy.

### **Introduction**

Cellulitis is associated with substantial patient morbidity and accounts for a large percentage of infections requiring hospitalisation.<sup>1,2</sup> In Ireland in 2009, 10,465 patients were admitted to hospital with cellulitis for a median of 4 days, of which 9,716 (92.8%) were admitted through the Emergency Department (ED).<sup>3</sup> Furthermore, in a point prevalence survey of 20 European hospitals, skin and joint infections were second only to pneumonia as the most common indication for inpatient antibiotic treatment.<sup>4</sup> Despite this, cellulitis is an understudied condition. Not only is its prevalence in Irish EDs unknown, there is a lack of research-based data to guide evidence-based patient treatment, particularly in the ED setting. What treatment guidelines do exist are derived from expert consensus studies.<sup>5-8</sup> The Clinical Resource Efficiency Support Group (CREST) guideline (see Table 1) is commonly used in the National Health Service (NHS) to guide the treatment of cellulitis.<sup>8</sup> This guideline stratifies patients according to co-morbidities and signs of infection, and recommends antibiotic treatment ranging from oral therapy in CREST Class 1 to intravenous (IV) therapy in CREST Classes 2-4. To the best of our knowledge, the clinical utility of this algorithm has not been prospectively assessed in the ED setting. The primary aim of this study was to measure the prevalence of cellulitis presenting daily to EDs in Ireland. The secondary aims were to determine: (1) the clinical utility of the CREST guideline in predicting the ED disposition of patients presenting with cellulitis; (2) preliminary clinical and epidemiological factors which may predict route of antibiotic therapy; and (3) prescribing practices for the ED treatment of cellulitis.

### **Methods**

This prospective, cross-sectional study was performed in the EDs of the Midland Regional Hospital Tullamore (MRHT), Midland Regional Hospital Mullingar (MRHM) and Midland Regional Hospital Portlaoise (MRHP)). The combined annual census of the three participating EDs is approximately 87,000. The Health Service Executive (HSE) Midlands Area Research and Ethics Committee approved the study. Consecutive adult patients aged > 18 years presenting with cellulitis over a one-month period (September 2011) were invited to participate and written consent taken. Cellulitis was diagnosed when any 2 of the following signs were present in anybody part: erythema, warmth, tenderness, swelling and regional lymphadenopathy. The treating ED doctor prospectively completed a study data collection form during clinical assessment. Demographic and epidemiological data on patient age, gender, patient referral source, previous episodes of cellulitis, pre-ED antibiotic treatment, and discharge or admission antibiotic treatment were taken. Assessment for local risk factors included examination for tinea pedis or evidence of interdigital maceration of the feet (athlete's foot), lymphoedema (defined as a chronic swelling of the leg with pre-morbid pitting

oedema), and venous disease (manifesting as venous ulcers, venous eczema and/or varicose veins). The presence or absence of general risk factors for cellulitis (BMI > 30kg/m<sup>2</sup>, diabetes mellitus, previously diagnosed peripheral vascular disease, chronic renal and liver disease, chronic steroid use and asplenia) was recorded. This clinical data was retrieved from the patient referral documentation (for example, General Practitioner [GP] ED referral letter), the patient history or any existing hospital chart at the time of patient recruitment to participate in the study. Information on location, size and duration of symptoms was also collected. Each patient was allocated to a disease severity class based on the CREST guidelines<sup>8</sup> by the treating doctor.

Descriptive statistics, odds ratios and classification and regression tree (CART) analysis were calculated. Logistic regression was used to model outcomes and find predictors for each of the outcome variables. Descriptive statistics and odds ratios were produced using SPSS statistical software (Version 20.0).

## **Results**

### *Prevalence of cellulitis*

Over the one-month study period there were 59 patients enrolled in total, 39 from MRHT, 18 from MRHT and 2 from MRHP. After excluding MRHP from the analysis due to poor patient recruitment at that study site, the prevalence of cellulitis attending the 2 remaining EDs was 12 cases per 1,000 ED visits (95% CI, 9-15 per 1,000 ED visits).

### *Patient Characteristics*

Forty patients were male (67.8%) and the mean age (which was normally distributed) was 50.9 years. Female patients were significantly older than males (mean = 60.9 versus 46.2 yrs;  $p = 0.019$ ). The majority of cases affected the lower limb ( $n=39$ , 71.3%). Overall, 27 (45.8%) patients were discharged on oral antibiotic treatment and 32 (54.2%) received IV antibiotic treatment. The majority were in CREST Class 1 ( $n=39$ ;66.1%); the remainder were in CREST Class 2 ( $n=20$ , 33.9%). There were no CREST Class 3 or 4 patients enrolled.

### *Predictors of ED discharge (see Table 1)*

In the multivariable logistic regression model, the following were predictive of oral antibiotic treatment: self-referral (OR = 6.2, 95% CI 1.9 – 20.0,  $p=0.03$ ), CREST Class 1 allocation (OR 6.81, 95% CI = 1.5-30.1,  $p=0.012$ ) and duration of symptoms over 48 hours (OR 1.2, 95% CI = 1.0-1.5,  $p=0.049$ ). Patients who had already received antibiotics prior to ED attendance (“Pre-ED therapy” group) were more likely to receive IV treatment (OR 0.22, 95% CI 0.06-0.8,  $p=0.04$ ). Seventeen patients (43%) in CREST Class 1 received IV antibiotics despite the guideline recommending oral antibiotic treatment. We attempted to produce a CART tree but this was not possible with the available set of predictors.

**Table 1 CREST classification for the management of cellulitis in adults<sup>8</sup>**

Class I	Class II	Class III	Class IV
Patients have no signs of systemic toxicity, have no uncontrolled co-morbidities and can usually be managed with oral antimicrobials on an outpatient basis	Patients are either systemically ill or systemically well but with a co-morbidity such as peripheral vascular disease, chronic venous insufficiency, or morbid obesity which may complicate or delay resolution of their infection	Patients may have a significant systemic upset such as acute confusion, tachycardia, tachypnoea, hypotension, or may have unstable co-morbidities that may interfere with a response to therapy or have a limb threatening infection due to vascular compromise	Patients have sepsis syndrome or severe life-threatening infections such as necrotizing fasciitis

**Table 2 Predicators of ED discharge with oral antibiotic therapy**

Variable	Odds Ratio	95% CI	P-value
ED self-referral	6.2	1.9-20.0	0.030
CREST class 1	6.81	1.52-30.58	0.012
Duration of infection >48 hrs.	1.22	1.0-1.49	0.049
Pre-ED antibiotic therapy	0.22	0.06-0.8	0.040

### *Prescribing practices*

Of the 27 patients discharged on oral antibiotics, 63% (17/27) received flucloxacillin combined with penicillin V, and 26% received flucloxacillin alone, with the remainder receiving clindamycin (n=1) or co-amoxiclav (n=2). There were 3 different prescribed doses of flucloxacillin and 4 different doses of penicillin V. Thirty-two patients received IV antibiotics: 27 received combined flucloxacillin and benzylpenicillin of 3 different doses, 3 received flucloxacillin and co -amoxiclav, 1 received co-amoxiclav alone and 1 received erythromycin alone.

### **Discussion**

This is the first study to measure the prevalence of cellulitis among patients in the ED setting in Ireland. The ED prevalence of cellulitis in this study was found to be approximately 12 per 1,000 ED attendances. This is also the first study to investigate the clinical utility of the CREST guideline in the ED setting. Patients who self-referred to the ED, who had not received antibiotic treatment in the community, who had a duration of symptoms exceeding 48 hours and who were in CREST Class 1, were more likely to be discharged from the ED on empiric oral antibiotic treatment. The majority of discharged patients (63%) were prescribed a combination of oral flucloxacillin and penicillin-V, while the majority of patients admitted to hospital (84%) received combined IV flucloxacillin and benzylpenicillin treatment.

It is recognised that there is a lack of research describing the epidemiology of cellulitis.<sup>9</sup> The existing published literature is limited by heterogeneity in terms of disease classification and description.<sup>10</sup> For example, prior to 2010 the term skin and soft tissue infection (SSTI) described a wide range of “uncomplicated” (cellulitis, impetigo, erysipelas, furuncle, simple abscess) and “complicated” (infected burn, deep tissue infection, major abscess, infected ulcer, perirectal abscess) infections.<sup>11</sup> In the United States, the Food and Drug Administration (FDA) Center for Drug Evaluation and Research recently recommended grouping erysipelas, cellulitis, major abscess and wound infection together as “acute bacterial skin and skin structure infections” (ABSSI) for the purposes of clinical trials.<sup>12</sup> Therefore, studies describing the prevalence of ABSSI may differ fundamentally from studies describing cellulitis or erysipelas alone.

Furthermore, since the International Classification of Diseases (ICD) coding does not distinguish between abscess and cellulitis, the true ED prevalence of cellulitis without abscess (“non-purulent cellulitis”) is difficult to estimate.<sup>13</sup> Bearing this in mind, prevalence data has shown that SSTIs

account for between 1.5 to 3% of ED visits in the USA and Canada<sup>14,15</sup>, and up to 3% of ED visits in the UK.<sup>16</sup> Given the recent epidemic of Community-Acquired Methicillin Resistant *Staphylococcus aureus* (CA-MRSA) infection in the USA<sup>17</sup>, the incidence of healthcare visits for SSTI has increased by 88% between 1997 and 2005.<sup>18</sup> Our data did not take account of the community-based treatment of cellulitis by GPs which has been shown to be up to 10 times higher than the recorded incidence in hospitalised patients in the Netherlands (12.1 per 100,000).<sup>19</sup>

Although ED doctors completed a separate CREST score for each patient, adherence to the guideline was poor with 17 patients (43%) in CREST Class 1 admitted to hospital for IV antibiotics, despite the guideline recommending oral treatment for this patient subset.

Marwick et al<sup>20</sup> also showed that 47% of admitted in-patients with cellulitis were in CREST Class 1, similarly indicating over-treatment of milder infections. There are many different contributory factors which influence the clinical decision to discharge or admit a patient presenting with cellulitis in the ED setting, including individual economic and social circumstances<sup>5</sup> as well as clinical impression (clinical gestalt) of infection severity. It is possible that many of these patients would have been suitable for either oral antibiotic treatment, a period of treatment in an ED clinical decision unit (CDU) or for outpatient antibiotic therapy (OPAT). It is therefore intuitively logical that a clinical prediction rule (CPR) derived and validated in the ED setting may be useful for the evidence-based ED management of cellulitis. In particular, an examination of characteristics predicting more than 24 hours of IV treatment would be helpful to differentiate patients requiring CDU or OPAT care from those requiring prolonged courses of inpatient IV antibiotic treatment.<sup>21</sup>

Other factors require further examination in a larger study. That patients describing over 48 hours of symptoms on ED arrival were more likely to be discharged may indicate a subgroup of indolent infection suitable for oral treatment. It is intuitive that patients who did not attend their GP prior to ED attendance were more likely to be discharged from the ED on oral antibiotics. Oral flucloxacillin and penicillin V were the most commonly prescribed antibiotics, with 63% of discharged patients receiving both. However, there is no randomised clinical trial (RCT) evidence to either refute or support this practice.<sup>22</sup> One small RCT showed no additional benefit when IV benzylpenicillin was added to IV flucloxacillin for the treatment of lower limb cellulitis.<sup>23</sup> This pilot study has some limitations. Firstly, the sample size is relatively small and the results may be imprecise. Secondly, we did not follow patients up beyond their ED admission and since we are unaware of any adverse events, we cannot comment on the validity of the CREST guideline in the ED setting. Thirdly, the generalisability of the findings may be limited by geographical factors; since both participating EDs serve mixed urban/rural populations and the findings may not be valid in urban (city centre) EDs.

The prevalence of cellulitis is approximately 12 per 1,000 ED attendances in Ireland. Predictors of treatment with oral antibiotics in ED patients with cellulitis include CREST Class 1, self-referral, duration of symptoms over 48 hours and the absence of pre-ED oral antibiotic therapy. Current prescribing practices for the treatment of acute cellulitis are disparate and not evidence-based. A CPR derivation study, performed and validated in the ED setting, may contribute to an evidence-based approach to the ED management of cellulitis.

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