# **Is Oral or Intravenous administration of antibiotics superior in the Treatment of moderate cellulitis?**

# Introduction

Cellulitis refers to a spreading bacterial infection of the skin and subcutaneous tissues(1). Related skin and soft tissue infections(SSTI) are a common cause of presentation to Emergency Departments(ED) worldwide, representing between 1.5-3% of ED presentations in the UK and North America(2,3). Overall, many of these patients will have an uncomplicated recovery following treatment initiation(4, 5) however there are small but significant rates of progression and complications including systemic sepsis and necrotising or deeper tissue infections(6, 7). Consequently, the diagnosis, risk stratification and treatment is of interest to emergency physicians, as well as the risk of complications.

In practice, these infections are commonly stratified by severity based on underlying patient risk factors(8), extent of symptoms and the presence or absence of a systemic inflammatory response at time of presentation(7, 9-12). Treatment is then guided by this risk stratification. This practice is supported by various regional expert (9, 10, 13). Accordingly, patients with uncomplicated local SSTI are commonly discharged on oral antibiotics. Patients with some risk factors or systemic signs are treated with short course intravenous antibiotics in an ambulatory care setting before being stepped down to oral therapy. Patients with multiple risk factors for complications or signs of severe systemic sepsis on arrival are admitted and treated with longer term intravenous antibiotics(9, 10, 13).

There are some limitations with this practice. Firstly, there is limited evidence to support the treatment recommendations of the expert guidelines(7, 13, 14). There is also evidence to suggest that clinicians overestimate the severity of infections and preferentially treat cellulitis with intravenous antibiotics, often in contradiction to these guidelines(12, 15, 16). Finally, the limited research available suggests that oral antibiotics may be underutilised in this condition and patients may be being treated unnecessarily with intravenous antibiotics(16). This approach has potential negative implications at a clinical, financial and resource level(17). Oral antibiotics are increasingly used preferentially in the treatment of a wide range of infections(18-21) , with intravenous antibiotics being reserved for patients unable to tolerate oral medications or with impaired absorption(22). While intravenous antibiotics are felt to offer superior pharmacodynamics(23, 24) , these advantages do not appear to be borne out in clinical practice. In contrast, oral antibiotics offer the obvious benefits of negating the need for intravenous access and associated complications, hospital based administration, as well increasing the flexibility of treatment for outpatient and ambulatory settings(25, 26) . These offer flow on benefits of reducing length of stay and overall healthcare costs(26).

Several studies have now examined the efficacy of oral intravenous antibiotics in treating cellulitis, with results indicating non-inferiority of oral treatment(27, 28) (29, 30) . A Cochrane Meta-analysis of 3 of these trials in 2010 concluded that oral treatment may in fact be superior(31). This finding however is based on small trials and agents which do not match with Australian antimicrobial prescribing guidelines for cellulitis. Our hypothesis was that we would be able to demonstrate the equivalence of oral antibiotics in our setting and further cement the role of oral antibiotics in treating cellulitis.

# Study Objectives

The aim of our study is to compare the safety and efficacy of oral and intravenous antibiotics in treating patients with moderate severity cellulitis in a population of ambulatory and short stay patients in the Northern Territory of Australia. Specifically we aim to address whether oral antibiotics are equally if not more effective at producing resolution of cellulitis in these patients. Secondary outcomes include rates of treatment failure, complications of treatment and patient length of stay.

# Methods

A single centre randomised, single-blinded trial will be performed in the Northern Territory of Australia. Royal Darwin hospital is a tertiary teaching hospital in Darwin and along with Palmerston Regional Hospital services the Greater Darwin Area, with a population of 142,000 people(32). Ethics approval will be sought from the Top End Human Research Ethics Committee. Informed consent will be obtained for all participants prior to participation.

## Protocol

Patients will be eligible for inclusion in the study if they are referred by emergency department medical staff for treatment of cellulitis with IV antibiotics. Cellulitis will be defined by the presence of acute dermal/epidermal inflammation lasting <5 days and of probable infective aetiology. Patients will be required to be aged ≥16 years and have at least one marker of moderate severity, either a marker of systemic inflammatory response (documented temperature >37.8c, tachycardia >90bpm, systemic symptoms inc. malaise, flu like symptoms, nausea and vomiting or elevated inflammatory markers) or a risk factor eg. Diabetes, homelessness, etc.

Patients will be excluded if they are unable to or decline consent; have mild cellulitis suitable for immediate discharge(limited area <10cm in longest axis, no risk factors, no systemic symptoms); cellulitis complicating trauma, intravenous drug use or recent (<30 days) surgical sites; periorbital cellulitis; immunosuppressed patients; morbidly obese patients; a diagnosis other than cellulitis or complicated cellulitis (severe sepsis, extensive bullous changes, abscess formation or suspected necrotising deep tissue involvement); vomiting precluding oral therapy or prior treatment with per protocol oral antimicrobials for >48 hours or parenteral antimicrobials. Location of treatment will be as per standard hospital protocols and will take place in the Extended Emergency Medicine Unit. Screening, enrolment and randomisation of patients will be undertaken by the referring clinician with the assistance of an inclusion checklist.

Assessment of consenting patients will be as per standard hospital protocols. Patient’s local and systemic symptoms will be documented on presentation. Local pain will be assessed based on a verbal rating scale. Initial and routine observations will be performed as per standard nursing practice. Staff will be discouraged from marking the area of cellulitis due to the poor correlation with improvement and risk of bias. Following inclusion, patients will be randomised by sealed envelope in a 1:1 ratio with a 10 block schedule to oral or intravenous therapy. As per local antimicrobial stewardship patients will receive either 1g Oral/IV Di/Flucloxacillin four times daily or 450mg Oral/IV Clindamycin three times daily for immediate penicillin hypersensitivity. The referring and assessing clinicians will be blinded to the route of administration however by necessity, patients and administering nurses will not.

Further assessment of patients will take place as per standard clinical practice. Treatment success will be defined as suitability for discharge as determined by treating clinician. Treatment success will facilitate step down to a completion course of oral flucloxacillin or clindamycin and discharge from hospital. Treatment failure will be need for inpatient admission and will occur if the patient develops complicated disease(as per exclusion criteria) of if patient is unsuitable for discharge following at least 4 doses of flucloxacillin or 3 doses of clindamycin as determined by treating clinician. Treatment failure will result in inpatient admission and change to intravenous flucloxacillin/clindamycin. Further assessment will take place by research team using file review and follow up structured telephone interview at 7 days post enrolment and will focus on complete resolution, complications, patient satisfaction and uncaptured treatment failure, eg. Re-presentation or admission.

## Outcome Measures

The primary outcome measure is treatment success as defined above. Secondary outcomes are treatment failure(including re-admission), patient satisfaction and complications of treatment(diarrhoea, IVC site infection, drug reactions). A predetermined review of preliminary data after 100 patients will be performed to assess for safety concerns.

## Statistical Analysis

The trial will be designed to assess the superiority of either oral or intravenous arms. Prior studies have oral treatment efficacy have identified a 15-20% failure rate. Prior Cochrane Meta-analysis demonstrated the RR of treatment failure between oral and IV of 0.84[95%CI 0.73-0.98] with a calculated standard error of 1.205(31). Based on this, a sample size of 412 was calculated for a treatment effect of 16% difference in the primary outcome using G\*power(33). This assumes a 90% power and a two sided a error of 0.05. Two-tailed T tests will be performed with a p value of 0.05 indicating significance. Patients lost to follow up at 7 days will be included in the primary outcome assessment but will not be included in other metrics.

# Ethical Issues

Ethics approval will be sought prior to commencement of the study. We anticipate the main issue will relate to clinician concern that randomising patients who would normally receive a short course of intravenous antibiotics to oral therapy may theoretically result in an increased rate of treatment failure. We feel that currently the evidence regarding the equivalence of oral antibiotics provides genuine equipoise regarding this concern. Also, we feel the current practice of potentially unnecessary administration of intravenous antibiotics in this population may lead to an increased risk of drug related complications(25). Finally, the exclusion of vulnerable patients and patients with severe sepsis or complicated cellulitis will avert any risk to patients who are already at increased risk of adverse outcomes. At our institution, admission of patients to the Extended Emergency Medicine Unit currently requires consultant approval and we feel this senior clinical oversight during the randomisation and assessment period will further help avert any potential risk.

Our patient population is one with increased prevalence of Community Acquired Methicillin Resistant Staph Aureus(34), as well as rare tropical infections such as Burkholderia Pseudomallei. The antibiotics we have chosen for our treatment arms will not provide coverage for these pathogens and this represents a potential risk for treatment failure and patient deterioration. Nevertheless, our chosen treatment arms are consistent with Antimicrobial Guidelines at our institution which take into account the regional variations pathogen prevalence(35). These pathogens also more commonly present with abscesses, which are excluded from our study population. There is some evidence to suggest that cellulitis treatment failure rates for beta –lactams have not increased despite increased prevalence of CA-MRSA(36) which also reaffirms the safety of our proposed treatment arms.

Adverse events and patient concerns will be specifically sought at the planned telephone follow up, allowing the early establishment of safety signals as well as patient satisfaction and feedback. This contact will also provide a further safety net for patients, who may be asked to return to the referring Emergency Department if there are any ongoing concerns.

# Dissemination of Results

Our goal is to use the results of this trial to inform and improve practice at our institution and to contribute to the body of evidence establishing the safety and efficacy of oral antibiotics. In light of this, we will present our findings both to our regional hospital network and opportunistically at national or international conferences. We aim to publish our findings in a national peer-reviewed journal. In addition to this, patients will be asked if they would like to receive the final study results as a lay summary or the final published manuscript.

# Limitations

The primary limitation of our study design is the short window of treatment provided prior to the determination of success/failure. This is a practical limitation due to the way the Extended Emergency Medicine Unit functions at our hospital and the need to ensure standardised practice in the way patients were assessed. A previous study found the mean time to treatment success was 1.29 days for the oral arm(28) and so our study will be assessing efficacy at 0.75-1 days and may therefore overestimate the risk of treatment failure.

The difficulty in blinding the administered route of administration will also potentially lead to bias, as although assessing clinicians will be blinded to the route of administration, the patient and treating nurses will not, potentially leading to the introduction of bias. This is unavoidable as the alternative of treating the oral arm with sham IV antibiotics exposes these patients to the small but unnecessary pain and risks of IV access. The follow up process may also contribute a risk of recall bias, however this is hopefully minimised by having follow up at 7 days rather than 28 days.

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