Study Protocol

Title: High-dose Cephalexin for Cellulitis: A Pilot Randomized Controlled Trial

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Trial Registration: clinicaltrials.gov NCT04471246

Roles and Responsibilities
Our team members come from the Department of Emergency Medicine and the Division of Infectious Diseases with support from the Ottawa Methods Center.

Dr. Krishan Yadav is Assistant Professor of Emergency Medicine, emergency physician and clinical epidemiologist. He is an **early career investigator** with a main focus on the management of cellulitis. He will oversee all aspects of the program.

Dr. Ian Stiell is Professor of Emergency Medicine, Distinguished Professor and Clinical Research Chair, Senior Scientist, OHRI, and recipient of a CIHR Foundation Grant. He has extensive experience successfully leading randomized controlled trials and will help oversee study design and methodology.

Dr. Debra Eagles is Assistant Professor of Emergency Medicine, emergency physician and clinical epidemiologist. She is an **early career investigator** and Associate Scientist, OHRI. She will provide input on study design and implementation, and assist with manuscript preparation.

Dr. Kathryn N. Suh is Associate Professor of Infectious Diseases in the Department of Medicine and the Associate Director, Infection Prevention and Control Program at The Ottawa Hospital. She will provide clinical expertise with respect to study design and analysis.

Dr. Jeff Perry is Professor of Emergency Medicine, Research Chair in Emergency Neurological Research, emergency physician and clinical epidemiologist. He will be an advisor for study design and implementation.

Dr. Monica Taljaard is Associate Professor, Epidemiology and Public Health at the University of Ottawa, and Senior Scientist, OHRI. Dr. Taljaard has extensive experience with standard and cluster randomized controlled trials. She will oversee the data analysis.

1. INTRODUCTION

Background

Uncomplicated, non-purulent cellulitis is an infection describing the subcutaneous tissue of the skin.[1] Group A streptococcus (*Streptococcus pyogenes*), β-hemolytic streptococci and methicillin-susceptible *Staphylococcus aureus* are the most common causative agents for non-purulent cellulitis. Patients typically present to the emergency department (ED) with pain, redness, swelling and induration of the affected skin. The borders of the reddened affected skin are irregular and patchy in patients with cellulitis. A minority of patients may exhibit signs of systemic illness, such as fever or tachycardia. The diagnosis of non-purulent cellulitis is clinical. Once the diagnosis is made, emergency physicians are expected to select appropriate antibiotic therapy. The physician must select the appropriate route (oral versus intravenous), agent, dose frequency and duration.

Burden of Disease

Cellulitis is a common condition diagnosed and managed in the ED and carries significant financial burden on healthcare systems globally. Extrapolating from US data[2], there are approximately 193,000 Canadian ED visits per year for cellulitis. Although Canadian data are lacking, a single Vancouver ED diagnosed 2234 patients with skin and soft tissue infections from 2003 to 2004, representing 2% of all ED visits.[3] A 2011 report by the Canadian Institute for Health Information found that cellulitis was the 5th most common reason for an ED visit in patients aged 45 to 64 years.[4] Cellulitis is responsible for a significant healthcare system burden due to hospital admission and subsequent costs. We conducted a health records review at The Ottawa Hospital Civic and General campuses, and found that 29.6% of all ED patients with non-purulent cellulitis are admitted to hospital.[5] A study in the United States reported an average cost of $8023 USD for hospitalized patients with skin and soft tissue infections with a mean length of stay of 4.9 days.[6]

Current Guidelines

Owing to a lack of high-quality evidence, published empiric treatment guidelines are largely based on expert opinion.[7-10] There are currently no Canadian guidelines for the management of skin and soft tissue infections. Despite the increasing burden of this common presentation, current evidence is lacking regarding the optimal management of cellulitis.

Oral Antibiotic Therapy: Cephalexin

The majority of ED patients with non-purulent cellulitis are treated with oral antibiotics and discharged home. Oral antibiotic therapy holds several advantages over the intravenous route, including lower risk of complications, decreased cost, and increased patient convenience and comfort.[11,12] We conducted a national survey of 391 emergency physicians, which revealed that the majority (89%) prescribed cephalexin as first-line oral antibiotic therapy for a duration of seven days to treat patients with non-purulent cellulitis.[13] The currently recommended dose range of cephalexin is 250mg to 1000mg QID (i.e. four times daily).[14] Infectious Disease Society of America guidelines for treatment of skin and soft tissue infections recommend cephalexin 500mg QID for a minimum of five days.[7] However, high-dose cephalexin (1000mg) achieves a higher peak serum concentration than standard-dose cephalexin (500mg), and reaches serum

concentrations that are comparable to parenterally (i.e. intravenous or intramuscular) administered cephalosporins.[15,16] Owing to its short serum elimination half-life (≤1 hour), cephalexin must be administered up to four times daily irrespective of the dose used.[16] With higher peak serum concentrations, administering high-dose cephalexin may lead to a reduction in treatment failures for patients with non-purulent cellulitis. Locally, infectious disease specialists in Ottawa recommend the use of high-dose cephalexin, but this is not based on high-quality evidence. There are no published studies evaluating whether high-dose cephalexin (1000mg QID) is superior to standard-dose (500mg QID) cephalexin.

Oral Antibiotic Treatment Failure

The oral antibiotic treatment failure rate in Canadian EDs is approximately 20%.[5,17,18] If an oral antibiotic treatment failure occurs, patients are typically switched to intravenous therapy and may require hospitalization. Intravenous therapy has many disadvantages, including patient inconvenience, patient discomfort, the added risk of intravenous line complications and higher cost. The current high oral antibiotic treatment failure rate may be due to suboptimal dosing of first-line oral therapy. We hypothesize that high-dose cephalexin may lead to ***lower rates of treatment failure*** and subsequently ***improved patient outcomes*** (fewer hospitalizations and avoidance of intravenous antibiotic complications).

2. RATIONALE

Before embarking on a large, multicenter trial, it is essential to conduct a smaller pilot to test and refine study procedures and demonstrate that it is feasible to proceed with a multicentre trial.

3. RESEARCH QUESTION & OBJECTIVES

The **ultimate goals** of this research are to reduce antibiotic treatment failure, return ED visits and use of outpatient intravenous antibiotics. The **specific goals** of this double-blind pilot randomized controlled trial are to (1) establish feasibility and refine study procedures before embarking on a larger, fully powered multicenter trial; and (2) generate preliminary evidence of effectiveness comparing high-dose to standard-dose cephalexin for non-purulent cellulitis.
Our **specific** objectives are to:
1. Measure feasibility outcomes, including recruitment rate, success of blinding and adherence; and
2. Measure patient outcomes, including oral antibiotic treatment failure rate and frequency of adverse events

4. METHODS

4.1 Design and Setting

We will conduct a parallel arm double-blind randomized controlled pilot trial at the Civic and General campus emergency departments (EDs) of The Ottawa Hospital. The study will operate seven days a week from 0800 to 2000, and will be conducted over a 6-month timeframe.

4.2 Study Population

4.2.1 Inclusion Criteria

Adults (age ≥18 years) with non-purulent cellulitis determined by the treating emergency physician to be eligible for outpatient care with oral antibiotics.

4.2.2 Exclusion Criteria

a) Age <18 years
b) Patient already taking oral antibiotics
c) Treating physician decides that intravenous therapy is required
d) Abscess requiring an incision and drainage or needle aspiration procedure
e) Known prior cellulitis secondary to methicillin-resistant *Staphylococcus aureus*
f) Cellulitis secondary to a human or animal bite wound
g) Surgical site infection
h) Malignancy and currently being treated with chemotherapy
i) Febrile neutropenia (temperature ≥38°C plus absolute neutrophil count <500 cells/μL)
j) Solid organ or bone marrow transplant recipient
k) Renal impairment with creatinine clearance <30 mL/min
l) Pregnant or breastfeeding
m) Allergy to cephalosporins or history of anaphylaxis to penicillin
n) Inability to provide consent

4.3 Orientation to Study

The following will be used to orient and educate ED staff to the study: i) research team to individually orient all emergency physicians and residents; ii) oral presentation at grand rounds; iii) periodic email; and iv) posters in ED physician work areas.

4.4 Patient Selection

A trained research assistant (RA) will identify potentially eligible patients during weekday business hours, and will be available on-call for after hours. The RA will approach the treating physician to discuss enrolling eligible patients. After confirming patient eligibility, the RA will explain the study details to the patient and obtain verbal informed consent. In addition, the RA will screen the ED patient log to identify missed patients.

4.5 Ethical Considerations

Ethical approval for the proposed study will be sought from the Ottawa Health Science Network Research Ethics Board (OHSN-REB). As both high-dose and standard-dose cephalexin are currently used in practice, we do not perceive any risks to patients or any ethical challenges in conducting this study.

4.6 Intervention and Comparator

The intervention is high-dose cephalexin (1000mg PO QID) for seven days. The comparator is standard-dose cephalexin (500mg PO QID) plus oral placebo for seven days. The duration of

therapy was chosen based on a national survey of the Canadian Association of Emergency Physicians.[13]

4.7 Allocation Concealment and Blinding

Eligible patients will be randomized (1:1) to high-dose versus standard-dose arms. The randomization sequence will be computer-generated by a statistician from the Ottawa Methods Center (OMC) using a randomly permuted block design with randomly varying lengths of 4 or 6, Allocations will be stratified by cellulitis location (lower limb vs. other). The research assistant will log into a secure web-based system managed by the OMC to determine the allocation for each patient who has consented and been enrolled. Cephalexin and placebo tablets will be encased in identical capsules, prepared and packaged independently by The Ottawa Hospital Pharmacy. The research assistant will verify the correct package for an enrolled patient with the ED nurse. The ED nurse will then dispense the study medications. The patients, treating physician and research team will be blinded.

4.8 Outcomes

Our pilot trial has both **feasibility** and (preliminary) **effectiveness** outcomes.

4.8.1 Feasibility Outcomes

The **primary feasibility outcome** is:

1. Patient recruitment rate (percentage of approached eligible patients who are successfully recruited) over 6 months. Our goal is to recruit at least 29% of eligible patients (see Sample Size)

The secondary feasibility outcomes are:

2. Ability to approach eligible patients (goal <10% missed)
3. Ability to blind patients using a questionnaire
4. Protocol adherence (i.e. fully adherent to allocated treatment for 7 days)
5. Loss to follow up at 14 days (goal <10% attrition)

4.8.2 Effectiveness Outcomes

The **primary effectiveness outcome** is:

1. ***Oral antibiotic treatment failure***, defined as a change in antibiotic (change in class of oral antibiotic or step up to intravenous therapy) within 7 days due to worsening infection, which is defined as:
    a. New fever (temperature ≥ 38.0°C) or *persistent* fever at Day 3 follow up; or
    b. Increasing area of erythema ≥20% from baseline; or
    c. Increasing pain ≥2 points from baseline (numeric rating scale)

The secondary effectiveness outcomes are:

2. Clinical cure (no erythema, pain and fever) at day 7
3. Clinical response (≥20% reduction in area of erythema compared to baseline) at day 3
4. Adverse events (e.g. vomiting, diarrhea, rash) at 14-day telephone follow-up
5. Unplanned i) return ED visits; and ii) hospitalization at 14-day telephone follow-up

Baseline clinical data will be recorded at the index ED visit. Patients will be assessed at a home visit by the research assistant on: 1) Day 3 (mid-therapy); and 2) Day 7 (end-of-therapy). If criteria are met for worsening infection, they will be sent to the ED for evaluation. If a home visit is not possible, the following alternate methods of follow up will be offered to patients:

1. Video follow up via a mobile device (tablet or phone) using FaceTime, Zoom or Skype. The patient must own a mobile device with one of these applications in order to proceed with this option. If this option is chosen, the patient will be given a disposable tape measure and disposable temperature strip so that they can measure the dimensions of erythema and temperature, respectively during the video follow up. The patient will be asked to download a free mobile application (Preventicus Heartbeats; https://www.preventicus.com/en/) that will allow the patient to measure their heart rate at the time of follow up.
2. Return to the ED for assessment. In this case, hospital parking fees will be reimbursed for the patient

Study participants will complete a questionnaire on Day 7 regarding effectiveness of blinding, medication adherence and adverse events.

4.9 Data Collection

Data will be collected by the research assistant at the index ED visit, and on follow-up visits (day 3, 7 and 14). Any paper files with identifying information will be kept separately and securely from all other study sites. These files will be kept in a locked filing cabinet in a locked office in an OHRI research office on F6 (Civic campus of The Ottawa Hospital). Data will be extracted from each record of treatment, which includes physician, nursing, consultant, triage, ambulance, and any consultation reports. This information will be obtained from hospital medical records (i.e. EPIC). Data will be entered into a secure web-based electronic data capture system. No identifying personal health information will be recorded into this system. Any potentially identifying information in the case record forms for each assessment plus the day 7 patient questionnaire are uploaded separately in the OHSN-REB application.

4.10 Data Management

The Ottawa Methods Centre will be responsible for creating and maintaining a secure web-based database (i.e. the electronic data capture system). The case record forms will be available in electronic format via the secure web-based database. The research assistant will then enter the relevant data directly into the secure web-based database. Paper copies of de-identified case record forms will be stored in a secure and locked filing cabinet on F6 (Civic campus) of the research floor at OHRI. A list of participant names and MRN will be kept in order to contact patients at day 7 and 14. This list will be kept on the TOH/OHRI cloud that is password protected with only the Principal Investigator and Research Assistant having access to the file. These files are kept separately from any de-identified study documents. All files will be destroyed after the required storage period according to TOH and OHRI policies.

4.11 Sample Size

For the full-scale trial, a minimum of 52 participants must be recruited annually per site (see Appendix). The Civic and General ED treats approximately 200 cellulitis patients with oral antibiotics annually.[5] If at least 180 patients can be approached per site per year, a minimum of 29% (52 participants) must be recruited at each site to meet the feasibility target. Based on previous experience with similar trials, we anticipate being able to recruit up to 35% of eligible patients. With 180 patients approached at each site, a 90% two-sided confidence interval around the anticipated recruitment rate will have a total width of 0.12, i.e. a lower limit of 0.291 and an upper limit of 0.413. Because the lower limit excludes the minimum feasibility target of 29%, we can be 90% confident that the future trial is feasible. Thus, our target sample size is 64 patients across both campuses over six months.

4.12 Data Analysis

Baseline demographic and clinical characteristics of participants will be described using descriptive statistics. Primary and secondary feasibility outcomes will be described using frequency and proportion with two-side 90% confidence intervals. Primary and secondary effectiveness outcomes will be described using frequency and proportion in each arm, together with 95% confidence intervals for the difference between the two arms. Analysis will proceed according to an intention-to-treat protocol.

While every effort will be made to avoid attrition, the prevalence of any missing data will be described in each arm and multivariable regression analysis will be used to identify baseline characteristics associated with attrition. Any identified characteristics will need to be adjusted for in the primary and secondary outcome analyses to avoid bias due to attrition. Single or multiple imputation will be used as sensitivity analysis to explore the implications of non-randomly missing data under extreme assumptions about attrition.

4.13 Data Monitoring

As this is a pilot study, we will not be utilizing a data monitoring committee or preplanned interim analyses. A research coordinator will conduct trial auditing monthly independent from the study investigators.

5. IMPORTANCE

Approximately 193,000 patients visit Canadian EDs each year for cellulitis.[2] If a pilot randomized controlled trial is successful in demonstrating feasibility, a larger multicentre trial has the potential to show that high-dose cephalexin is a cheaper, less-invasive option compared to intravenous antibiotics. This work has the potential to demonstrate a meaningful reduction in treatment failures for this common clinical problem. This pilot study will be the first to compare high-dose cephalexin to standard-dose cephalexin for ED patients with non-purulent cellulitis. The results of this pilot randomized trial will help inform the design and implementation of a larger, multicenter randomized controlled trial to answer this important clinical question.

6. STUDY ORGANIZATION, ETHICS AND DISSEMINATION

The first five months will be dedicated towards obtaining OHSN-REB approval, study orientation and education for ED staff, and working with the TOH pharmacy for study medication preparation. Over six months, we will enroll patients for this randomized controlled trial. Data analysis will then be conducted followed by manuscript preparation.

Milestone	**Timeline**
Target start date:	04/2020
Hire research staff	05/2020
OHSN-REB approval	03/2020 – 05/2020
Study detail education for ED members	05/2020
TOH Pharmacy study medication preparation	05/2020
Database creation	04/2020 – 05/2020
Patient enrolment	06/2020 – 12/2020
Data analysis	12/2020 – 03/2021
Target end date:	04/2021

6.1 Protocol Amendments

The findings from this pilot study to determine feasibility may reveal certain protocol modifications are necessary for an optimally conducted future multicentre trial. Any modifications for a future larger scale trial will be communicated by the primary investigator to all other investigators and such changes will be reflected in any research ethics board submissions.

6.2 Informed Consent

The emergency physician will inform the patient about the study (i.e. we are assessing two different approved doses of the most commonly used antibiotic for cellulitis) and will ask for permission to allow a research assistant to speak with the patient about the study. If permission is granted, the emergency physician will delegate the task of obtaining oral consent (i.e. structured script read to the patient and ability to answer any questions the patient may have) using the integrated consent model to the research assistant. The integrated consent model has been chosen as the two treatment doses being evaluated are currently used in practice by doctors when treating cellulitis. The approved dosing range for cephalexin is 1g to 4g daily. Therefore, we anticipate minimal risk to patients who decide to participate in the trial, and the integrated verbal consent approach allows for a robust and practical approach to the consent process in the Emergency Department setting.

The research assistant will be trained to obtain oral consent using an OHSN-REB approved script. Once the discussion is complete, the research assistant will document the discussion and patient decision on the study page under the research section of the Epic electronic health record. The patient will be provided with an information sheet that includes study information. The informed consent script and patient information sheet are uploaded separately within the OHSN-REB application.

6.3 Confidentiality

Participant confidentiality and privacy is strictly held by the principal investigator and the staff. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. All research activities will be conducted in as confidential a manner as possible. Authorized representatives of the OHSN-REB, or OHRI may inspect all documents and records for audit purposes.

6.4 Declaration of Interests
All study investigators have no financial or competing interests for this study.

6.5 Access to Data
Dr. Yadav and his study team will have access to information collected about the identity of participants, The OHSN-REB and OHRI will be granted direct access to the participant's study files for verification of clinical trial procedures and data should it be requested for audit purposes.

6.6 Ancillary and post-trial care
Not applicable.

6.7 Dissemination policy
The investigators plan to present the study results at an annual Emergency Medicine scientific meeting and aim to publish the results in peer-reviewed journals. Study participants will be given contact information for the principal investigator and will be encouraged to contact the research team should they wish to be informed of the study results. All study results will also be made available on clinicaltrials.gov. All results will keep the identity of all participants confidential and no identifying data will be published.

Appendix A. Preparatory Work

A. Preliminary Sample Size for Future Full-Scale Trial

The estimated treatment failure rate with standard-dose cephalexin is 20%. For a multicenter trial, a total of 2552 participants are required to achieve 90% power to detect a minimum important difference of 5% in treatment failures in the high-dose cephalexin versus standard-dose cephalexin arm. We plan to conduct the full-scale trial at 20 centres over 2.5 years, which would require a minimum recruitment of 52 participants annually per site. Our research group has established relationships with >20 Canadian EDs where we have previously conducted successful studies.

B. National Survey of ED Physicians

We surveyed 391 Canadian emergency physicians to identify how cellulitis is treated in the ED.[13] The most commonly prescribed oral antibiotic is cephalexin and the most common duration is 7 days.

C. Local Survey of ED Physicians

We surveyed 57 emergency physicians at The Ottawa Hospital (67% response rate). Physicians were asked two questions:

1. "If a randomized trial was conducted comparing high-dose (1000mg) to standard-dose (500mg) cephalexin for adults with cellulitis, would you be willing to enrol patients into this study?" **98.2%** stated **YES**

2. "If high-dose cephalexin is shown to be superior to standard-dose cephalexin for treating cellulitis, would you use high-dose cephalexin?" **100%** stated **YES**

The results of this survey confirm that the physicians in our ED are willing to enrol patients for this planned randomized controlled trial.

D. Defining Oral Antibiotic Treatment Failure

There is no validated uniform definition of antibiotic treatment failure. We conducted a systematic review to examine treatment failure definitions for patients with non-purulent skin and soft tissue infections in the literature.[19] The findings of this review were used to develop a robust, clinically meaningful definition of oral antibiotic treatment failure.

8. REFERENCES

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