Intravenous cefazolin plus oral probenecid vs. oral cephalexin for the treatment of cellulitis: a randomized controlled trial

STUDY PROTOCOL

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www.clinicaltrials.gov (ID number: NCT01029782)

Research Significance

This project will evaluate the efficacy and safety of oral cephalexin compared to intravenous cefazolin plus oral probenecid for the treatment of uncomplicated skin and soft tissue infections (SSTIs), in patients that present to the Emergency Department (ED). We will attempt to identify if this patient population, which would under current Canadian practice patterns, be treated as ambulatory patients receiving cefazolin and probenecid, are able to be managed with oral antibiotics at home. It is our belief that, by establishing the equivalent efficacy and safety of these two antimicrobial regimens that in patients who present to the ED with SSTIs many more patients will be successfully treated at home rather than need to return to the ED daily. This will allow many patients to be treated without disruption of their normal daily activities (e.g. work, school) and will potentially reduce the overwhelming burden of ED overcrowding and overall healthcare costs. Results of our study will be used to inform patients, clinicians, researchers and policy makers on optimizing care for patients with mild-moderate SSTIs and ultimately to improve patient care throughout Canada.

Project Abstract

Skin and soft tissue infections (SSTIs) are a common reason for presentation to an Emergency Department (ED) in Canada. Although many patients with mild SSTI are able to be managed at home with oral antibiotics, those with mild-moderate infections are often treated with parenteral antibiotics. Current practice patterns in Canadian EDs indicate this patient population is often treated with intravenous cefazolin once daily along with oral probenecid and return to the ED or other ambulatory setting for daily medication administration and assessment. This parenteral regimen has been found to result in success rates comparable to studies which have evaluated treatment success with oral antibiotics in this patient population (89-97%). Although successful outcome can be achieved with this approach, it is often inconvenient for the patient to return to the ED/ambulatory care unit daily and does contribute to overall ED/ambulatory care visit volumes and overall health care costs. Unfortunately, there has never been a study which has evaluated the relative efficacy and safety or oral antibiotics to the aforementioned parenteral approach in this patient population and thus there remains a significant knowledge gap which must be addressed before a change in current practice can be explored. The objectives of the study is to determine whether oral cephalexin is equivalent to intravenous cefazolin plus oral probenecid for the treatment of uncomplicated SSTIs in patients that present to the ED. This study will be a prospective, multi-centered, randomized controlled non-inferiority trial comparing cephalexin 500 mg orally four times to cefazolin 2 g IV plus probenecid 1 g orally, in patients presenting to the ED with presumed diagnosis of mild to moderate SSTI. The primary outcome will be to compare the proportion of patients failing therapy for their cellulitis after 72 hours of antibiotic treatment with oral cephalexin or IV cefazolin/oral probenecid 1 g daily. Secondary outcomes include the clinical cure rate at 7 days, percentage of patients requiring hospital admission, percentage of patients stepped down to oral antibiotics on or before day 7 of therapy, percentage of patients requiring an additional antibiotic prescription on day 7, and the frequency of adverse events.

Background and Rationale:

Skin and soft tissue infections (SSTIs) include infections in any layer of the skin, subcutaneous tissue, fat and muscle. Cellulitis is the most common type of SSTI defined as an infection of the dermis and subcutaneous tissue that is characterized by symptoms such as pain, tenderness, swelling, induration, purulent drainage or discharge, erythema, and/or localized warmth. Gram-positive cocci are the causal pathogens in the majority of cellulitis cases, specifically *Staphylococcus aureus* and streptococci.[1,2,3] The prevalence of cellulitis is difficult to measure and published data is limited. Approximately 7-10% of hospitalizations in North America are a result of skin and soft tissue infections [4] and the estimated cellulitis (ICD-9 codes 681.0-682.9) incidence rate is 24.6/1000 person-years with an increased prevalence in males and in patients aged 45 to 64.[5,6] An estimated 20.5% of cellulitis cases are seen in acute care settings such as EDs and outpatient hospitals.[6]

Although many patients with mild SSTI are able to be managed at home with oral antibiotics, those with mild-moderate infections are often treated with parenteral antibiotics. Current practice patterns in Canada EDs indicate this patient population is often treated with intravenous cefazolin once daily along with oral probenecid and return to the ED or other ambulatory setting for daily medication administration and assessment.[7] Although cefazolin is traditionally administered every 8 hours, the use of probenecid allows for once daily administration of cefazolin by inhibiting renal secretion, slowing renal elimination and prolonging the period of therapeutic serum concentrations. Brown et al. found that serum concentrations of cefazolin achieved following probenecid administration were sufficient at 24 hours to exceed the minimum inhibitory concentration (MIC) of cefazolin for *Staphylococcus aureus* and streptococci, and at 12 hours to exceed the MIC for Gram-negative pathogens normally sensitive to cefazolin, such as *Klebsiella pneumoniae, Escherichia coli,* and *Proteus mirabilis."*[8] A small pharmacokinetic study was then conducted comparing cefazolin 2 g IV every 8 hours or 2 g IV once daily with

probenecid 500 mg orally four times daily, where they found that there was no significant difference between peak cefazolin concentrations on day 1 and 5.[9]

A systematic review of the literature has been previously performed by a member of the investigative team.[10] There have been only two studies performed to date which have evaluated clinical outcomes in patients treated with cefazolin and probenecid for the management of SSTI. Brown et al performed a prospective, randomized, double-blind study involving 194 patients compared the efficacy of ceftriaxone to cefazolin with probenecid in the treatment of SSTIs.[11] Results indicated there was no significant difference in failure rates between the two treatment arms between ceftriaxone and cefazolin/probenecid at 7% and 8%, respectively (p=ns).

In a second study by Grayson et al. performed a prospective, randomized, double-blinded study in 132 patients to evaluate the efficacy of once-daily cefazolin with probenecid compared to ceftriaxone for the management of moderate-severe cellulitis.[12] Patients were given 1 g probenecid or placebo orally, followed 10-15 minutes later with 2 g IV cefazolin or ceftriaxone, respectively. A clinical cure was achieved at the end of therapy in 51 of 59 cases (86%) treated with cefazolin plus probenecid and 55 of 57 cases (96%) treated with ceftriaxone plus placebo, p=ns.

This parenteral regimen of single daily cefazolin and probenecid has been found to result in success rates which are comparable to studies that have evaluated treatment success with oral antibiotics in this patient population (89-97%).[2,13,14,15] Although successful outcome can be achieved with this approach, it is often inconvenient for the patient to return to the ED/ambulatory care unit daily and does contribute to overall ED/ambulatory care visit volumes and overall health care costs. Unfortunately, there has never been a study which has evaluated

the relative efficacy and safety of oral antibiotics to the aforementioned parenteral approach in this patient population and thus there remains a significant knowledge gap which must be addressed before a change in current practice can be explored.

Research Question

The question this study will seek to answer is:

Is cephalexin 500 mg orally four times daily equivalent to cefazolin 2 g IV daily plus probenecid 1 g orally daily in the management of uncomplicated mild-moderate skin and soft tissue infections in patients presenting to the emergency department?

Objectives

Primary Objective

To compare the proportion of patients failing antibiotic therapy after 72 hours of treatment between the oral cephalexin and intravenous cefazolin plus probenecid arms.

Secondary Objectives

To compare the cure rate of antibiotic therapy at 7 days between the oral cephalexin and intravenous cefazolin plus probenecid arms.

To compare the percentage of patients requiring hospital admission between the two study groups, at any point during the study.

To compare the number of patients stepped down to oral therapy over the study period, between the two treatment arms.

To compare between the two studies arms, the number of patients requiring an additional prescription, prescription type and why they are requiring the prescription on day 7 of therapy.

To compare the frequency of adverse events during the study period in each arm.

Methodology

Setting and Design

The study will be a prospective, multi-center, double-blind, randomized controlled non-inferiority trial evaluating oral cephalexin compared to intravenous cefazolin and oral probenecid for the treatment of mild-moderate cellulitis in patients presenting to the ED. The study will be conducted in the ED at both the Kelowna General Hospital (KGH) and Queen Elizabeth II Health Sciences Center (QEII HSC) Halifax Infirmary (HI). KGH is a 350 bed tertiary care teaching hospital affiliated with the University of British Columbia. The KGH ED has an annual ED census of 56,000 patients. The QEII HSC is a 1034-bed adult tertiary care and referral center within Capital Health and teaching hospital affiliated with Dalhousie University. The HI has an annual ED census of 62,000 patient visits. Ethics approval for this study is currently being sought through the Interior Health Research Ethics Board, the University of British Columbia Clinical Research Ethics Board and the Capital Health Research Ethics Board. Patient consent will be sought for eligible patients. (See Appendix IV)

Patient Selection

Patients will be considered for inclusion into this study if they present to KGH or QEII HSC ED Monday to Friday between 0800h-1600h with presumed diagnosis of mild-moderate SSTI and they are deemed well enough to be treated as outpatients. The planned recruitment period is

May to October 2010 which, based on historical data from both centers will allow for sufficient time to enrol the desired sample size.

There are no known validated grading tools to determine the severity of a specific patients cellulitis. Due to this factor, this trial was designed to closely mirror “real life practice” where there is some inter-physician variability in determining the severity of cellulitis and subsequent treatment. To decrease this variability we have used objective criteria to exclude patients with the most mild and most severe cases of cellulitis. For example, patients who require only oral antibiotics (mild cellulitis) and patients who meet the criteria for sepsis (severe cellulitis) will be excluded.

Inclusion criteria include, (i) males and females 19 ~~-~~ years of age or older; (ii) patients having 2 or more of the following symptoms: pain/tenderness, fever, swelling, erythema, localized warmth, purulent drainage/discharge, induration, regional lymph node swelling or tenderness, and/or extension of redness; and (iii) believed to be secondary to an infection; (iv) can be treated as an outpatient and return daily to the Emergency Department.[13] Exclusion criteria include: (i) patients in which oral antibiotic therapy are indicated but intravenous antibiotics are not required~~known allergy to study drugs~~; (ii) known chronic kidney disease with a creatinine clearance <30 mL/min; (iii) known previous methicillin-resistant staphylococcus aureus (MRSA) infection; (iv) use of antibiotics for greater than 24 hours in the past 7 days prior to study enrolment; (v) wound/abscess requiring operative debridement or incision and drainage; (vi) suspected necrotizing fasciitis, osteomyelitis or septic arthritis; (vii) febrile neutropenia; (vii) concomitant documented bacteremia; (viii) two or more signs of systemic sepsis: temperature >38°C or <36°C; heart rate >90 beats/min; respiratory rate >20 breaths/min; WBC <4,000 cells/mm³ or >12,000 cells/mm³ or >10% band forms (if available, but not necessary); (ix) new altered mental status; (x) infections at a site involving prosthetic materials; (xi) animal or human bite wound infections; (xii) post-operative wound infections; (xiii) known peripheral vascular

disease; (xiv) superficial thrombophlebitis; (xv) pregnant/breastfeeding; (xvi) obesity (BMI > 30 kg/m^2); (xvii) known allergy to study medication.~~.~~

Intervention

Eligible patients will be randomized to one of two treatment groups using a double-dummy blind approach. One treatment group will receive therapy with cephalexin 500 mg orally four times daily plus saline IV and oral probenecid placebo daily and the second treatment group will receive therapy with intravenous cefazolin 2 g IV plus probenecid 1 g daily plus cephalexin placebo orally four times daily. Probenecid or probenecid placebo will be administered 20-30 minutes prior to the administration of cefazolin. Cefazolin will be administered by slow IV bolus over 3-5 minutes.

Outcome Measures

The primary outcome of this study is the proportion of patients failing therapy after 72 hours of antibiotic treatment with oral cephalexin or intravenous cefazolin plus oral probenecid. Failure is defined as hospital admission, change in antibiotics (not due to allergy), or persistent or worsening signs and symptoms of cellulitis following at least 72 hours of antibiotic therapy, to be assessed between 72 and 96 hours after antibiotic therapy is started. Hospital admission or a change in antibiotics (not due to allergy) less than 72 h after the initial ED visit will also constitute treatment failure.

Secondary outcomes include the clinical cure rate of cellulitis after 7 days of antibiotic therapy, The percentage of patients requiring hospital admission at any point during the study, the percentage of patients stepped down on or before day 7 of therapy, the percentage of patients requiring an additional antibiotic prescription, what antibiotic and why on day 7, and the frequency of adverse events in the study population during the study period.

Study Procedures

Eligible patients presenting to the ED with presumed SSTI who are well enough to be treated as outpatients, will be approached for enrolment. A research assistant will obtain written informed consent on the form found in Appendix IV. Patients who do not give written consent or those who meet any one or more of the exclusion criteria will not be enrolled in the study.

During the initial ED visit, each patient that is enrolled will be assigned a unique study number. Study numbers will be randomized in blocks of eight and stratified according to each center to either treatment group via a randomized computer sequence prior to the start of the study by the KGH pharmacy manager who will keep this information in a sealed enveloped confidential locked in a filing cabinet within the pharmacy department. The respective in-patient pharmacy will be informed of each patient's study number upon enrolment and will dispense the corresponding treatment box with the intravenous medication prepared, labelled only with the study number. Patient demographics and clinical data will be collected using a standardized data collection form. Data collected will include: (i) recruitment site; (ii) age; (iii) gender; (iv) weight; (v) past medical history; (vi) current medications; (vii) location of cellulitis; (viii) duration of infection prior to ED visit; (ix) any antibiotic therapy in the last 7 days; (x) social history (recreational drug use, alcohol); (xi) IV drug use; (xii) homelessness; (xiii) previous contact with the health care system over the past year.

To preserve confidentiality and anonymity, the data collection form will be labelled only with the study number assigned to the patient upon enrolment and will not contain patient identifiers, including patient initials or medical record number. Collected data will be stored in binders that will be kept in a locked cabinet in a locked office that only the investigators and research assistant have access. Completed consent forms will also be stored in these binders. Any data

that will be electronically recorded, such as information being transferred to an Excel spreadsheet, will be saved in a file folder with select permissions for the investigators only. Both print and electronic data will be preserved for a minimum of 25 ~~25~~ years in these locations. The study investigators will destroy the data after 25 ~~25~~ years, by shredding the files or double-deleting the information from the computer.

Study drug boxes for both treatment groups will be prepared by the study investigators at a single site (KGH) and then those required will be shipped to QEII HSC. The drug boxes for the first treatment group (A) will contain enough drug for 7 days of therapy with cephalexin 500 mg four times daily as well as for 7 days of placebo IV cefazolin and placebo probenecid daily. The drug boxes for the second treatment group (B) will contain enough drugs for 7 days of therapy with 2g IV cefazolin and 1 g probenecid daily as well as for 7 days of placebo cephalexin four times daily. The cefazolin and placebo syringes as well as the patient's vial of probenecid or placebo capsules will be kept in the minor treatment fridge in the respective emergency departments for the duration of the patient's treatment.

At the initial visit, 28 tablets of cephalexin 500 mg (group A) or placebo (group B) will be given to the patient in a vial to self-administer at home four times daily (Figure 1). Patients will be required to return to the Emergency Department daily for assessment and treatment with IV placebo with oral placebo (group A) or IV cefazolin and oral probenecid (group B). Patients will be instructed to bring in all medication with them every day to the emergency department. The number of tablets left in the vial at study completion will be assessed by the research assistant or study investigator.

Daily intravenous treatment and assessment of signs and symptoms will continue until 72 hours have passed from the first dose of study drug. If, during any assessment occurring in the first 72

hours, the managing physician feels that a change in antibiotic therapy or hospital admission is required, the patient will be considered a treatment failure and will be unblinded from the trial. In all other cases, clinical success and failure will be assessed during the ED visit occurring between 72 and 96 hours after the first study dose. If the patient has persistent or worsening signs and symptoms, or requires hospital admission or a change in antibiotics, they will be considered a treatment failure and their therapy will be unblinded at that visit. If the patient satisfies the requirements for step-down from IV to oral antibiotic therapy, they will be considered a treatment success, the physician will write an order for oral antibiotics, and their therapy will be unblinded at that visit. Clinical experience and limited research suggest that a switch from intravenous to oral antimicrobial agents can be safely made after 3 to 4 days.[1] If patients are not returning to the ED on day 7, they will be contacted by telephone to assess 7 day cure rate based on signs and symptoms of their cellulitis, visits a physician or emergency department. If the patient is not a clinical failure but does not meet the requirements for step-down from IV to oral antibiotic therapy, they will continue on the study drug and return daily for IV therapy and assessments until either success or failure can be determined, up to 7 days after the first dose of study drug. As it has been shown that 5 days of antibiotic therapy is as effective as 10 days of therapy in the treatment of uncomplicated cellulitis [16], we feel that 7 days of therapy will be an adequate length of time during which treatment success or failure can be accurately determined.

Evaluation of Study Outcomes

Patients will receive study cards and be instructed to present these at each visit to the triage nurse, who will call the number on the card to notify the research assistant of the patient's arrival. A study summary sheet will be placed on the patients chart (Appendix IV). The data collection form found in Appendix I will be used for the initial Emergency Department visit and up

to 6 additional data collection forms (Appendix II) will be completed at each subsequent visit by the research assistant.

Presence of the following signs and symptoms will be recorded and include pain/tenderness using a visual analog scale, swelling, erythema, localized warmth, purulent drainage/discharge, induration, regional lymph node swelling or tenderness, extension of redness, temperature, heart rate, blood pressure and respiratory rate.

During the initial visit, demographics, clinical history and baseline signs and symptoms of each patient will be recorded by the research assistant. At each subsequent assessment, the presence of signs and symptoms will be recorded and used to determine the efficacy of antibiotic therapy. The resolution of signs and symptoms will be part of the criteria used to determine treatment success and the persistence of signs and symptoms will be part of the criteria used to determine failure. The data collection form will also have an area in which the physician's plan will be recorded. Options will include: (i) continue study drug therapy; (ii) step down from IV to oral therapy; (iii) change antibiotic therapy; and (iv) admit to hospital. The research assistant will assess compliance with oral therapy at end of study using the number of capsules remaining in each patient's vial and an exit survey will be conducted to assess blinding of both patients and physician on that day (Appendix III). After the blinding assessment is completed, the patient may be informed which study treatment they received. If the patients is stepped down to oral therapy and is not returning to the ED on day 7 for assessment, the research assistant will contact the patient for a telephone interview to ask about: (i) any visit to a physician since discharge, and why; (ii) any visit to an ED, and why; and (iii) signs and symptoms of their cellulitis including: pain/tenderness, fever, swelling, erythema, localized warmth, purulent drainage/discharge, induration, regional lymph node swelling or tenderness, and/or extension of redness (Appendix III).

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Statistical Analysis

Using a clinically important difference of 10%, a two sided alpha of 0.05, and 80% power, 157 patients would be required in each arm. This calculation assumes an 85% cure rate in each group.[12] The data from the collection forms will be entered into an Excel spreadsheet for analysis. Patients will be analyzed on an intention to treat basis as the primary endpoint. A per protocol analysis will also be conducted as a secondary endpoint if necessary. Descriptive statistics will be used to describe patient demographic information, the primary outcome, and the secondary outcomes. The *t*-test for independent groups (if data are parametric) or the Mann-Whitney test (if data are non-parametric) will be used to compare continuous data and the Fisher's test for discrete data. Patients that are lost to follow-up will be assumed to have failed therapy. There are no interim analyses planned for this study given the short enrolment period and interventions that are already well established in the treatment of skin and soft tissue infections.

Study Timeline

Objective	**Date**
Ethics Application (3 ethics boards)	October 1, 2009
CHSP Grant Application	October 16, 2009
Assembly of study drug boxes (Investigators)	February-Mar 2010
Random Number Generation (Independent Pharmacy Contact)	Feb-Mar 2010
Shipment of study drug boxes to Halifax	April 2010
Informing ED Physicians -initial information on potential study	Sept 2009

-once approved, full information and education on study protocol, roll-out, study timeline — March 2010

Dissemination Plan

We propose to use a multi-layered approach for knowledge exchange and dissemination which will involve: (i) targeted communication with both internal and external stakeholders; (ii) academic publications and presentation; and (iii) project development.

(i) Targeted Communication with Key Stakeholder Groups: A one page summary highlighting key findings and messages will be developed with information tailored (increasing detail, complexity and technical specialization) for internal and external stakeholders which will include but not be limited to physicians (partcularly family practitioners and emergency physicians), pharmacists and hospital administrators. Distribution will occur through family physician offices, emergency departments and professional associations. Results will be presented to the Pharmacy and Emergency Medicine communities through Grand Rounds presentations.

(ii) Academic Publications: We will present our findings at provincial (e.g. Dalhousie University Annual Refresher Courses for both Medicine and Pharmacy) and national (e.g. Canadian Society of Hospital Pharmacists (CSHP) and Canadian Association of Emergency Physicians (CAEP) venues. We will also prepare one medical (e.g. Canadain Journal of Hospital Pharmacy or Canadian Medical Association Journal) and one methods based (e.g. American Journal of Epidemiology or Canadian Pharmacy Journal) manuscript for high-impact readership.

(iii) Project Development: Study results will be integral to future project development. We plan to use the findings from this study to design further studies to further explore opportunities to improve care in this patient population.

Relevance

This study will represent the first prospective study ever performed to evaluate the relative efficacy and safety of cephalexin compared to cefazolin plus probenecid in the management of SSTI in patients presenting to the ED. In this regard this study is unique and necessary to ensure optimal care is being provided to this patient population. These results will also lay the foundation for future studies in this area.

If our results demonstrate that in this patient population oral antibiotics are equivalent to parenteral antibiotics in the outpatient management of SSTI, these findings will be applicable in all jurisdictions throughout Canada and have significant impact in current practice. If the management of SSTI is further shifted to care at home with oral antibiotics there are several additional intangible benefits from this work. First, it may place further increased attention and focus on optimal prescribing, best pharmacotherapy practice and drug therapy monitoring in this patient population. Second, the ability to shift care to home rather than in the ED or ambulatory care setting, should improve overall patient satisfaction and result in less disruption to patient daily activities (e.g. work, school). Finally, care at home with oral antibiotics for this patient population may help reduce the ever-growing problem of ED overcrowding and overall heath care costs.

Budget Justification

A. PERSONNEL ($12,977) ($11,577 Requested)

1. Research Assistants(s) ($10,577)

This study will require two research assistants using senior pharmacy students. Each center will require 0.5 FTE student for 16 weeks. Research assistants will be required for this study to carry out the described methodology including patient enrollment and follow-up. The current rate of pay for Interior Health Authority for student research assistant inclusive of all benefits, for 16 weeks at 36 hours/week at 0.5 FTE ($5668). The current rate of pay for QEII HSC for a student research assistant inclusive of all benefits is $14.00/hour. For 16 weeks at 36 hours/week at 0.5 FTE ($4200). In addition, one student research assistant will be required in IHA for 36 hours to prepare study drug kits. At $19.68/hour x 36 hours ($709). Overall research assistant costs would be $9641.

2. Research Coordinator ($1,400) ($0 Requested)

Support from a Research Coordinator from the Department of Emergency Medicine, Dalhousie University. This position will provide administrative support to the principal investigators and research assistants throughout the study. Salary for this position as per Dalhousie University Collective Bargaining Agreement (CBA) at $35 per hour for 40 hours is $1400 but will be provided in-kind as part of existing infrastructure.

3. Statistical Analysis ($1,000)

Support for statistical analysis will be contracted to a PhD-trained statistician. Cost estimate comprised of statistical consultation and technical support at standard rate of $100 per hour as per the Biostatistical Consulting Service in the Department of Community Health and Epidemiology, Dalhousie University for 10 hours ($1000)

B. Drug Costs ($6284.00) ($3142 Requested)

Drug costs consist of acquisition, preparation and packaging of all study medications and associated materials. Drug costs consist of cephalexin 500 mg tablets ($522), cephalexin placebo ($269), probenecid 500 mg tablets ($445), probenecid placebo tablets ($135), cefazolin 2g vials ($1904) and cefazolin placebo ($1076). Total drug cost $4351. Supplies to prepare and package study drug and placebos include capsules ($745), vials ($128), syringes ($420), boxes for study kits ($640). Total supplies ($1933) and total drug and supplies $6284. IHA will provide

in-kind funding for 50% of drug costs, capsules, vials & syringes ($3142) reducing costs for drug and supplies to $3142.

C. MATERIALS AND SUPPLIES ($400)

These items would include preparation of study materials, advertisements, miscellaneous office supplies, stationary and photocopying, courier charges, mailing expenses and long distance telephone. ($400)

D. RESEARCH EQUIPMENT ($3,000) ($0 Requested)

The overall costs include one personal computer, printer and software (MS Office for Mac) ($3000 Provided) which will be provided by existing infrastructure of the Department of Emergency Medicine at QEII HSC.

E. OTHER ($2,000) ($0 Requested)

1. Data Management ($2,000) ($0 Requested)

Data management costs will be provided in-kind by the Department of Emergency Medicine, IHA ($2000 Provided).

Total Required: $24,661

Total In-Kind: $9,542

Total Requested: $15,119

Acknowledgements:

Thank you to Leah Neumann, KGH 3rd year UBC summer student for assisting with drafting the protocol.

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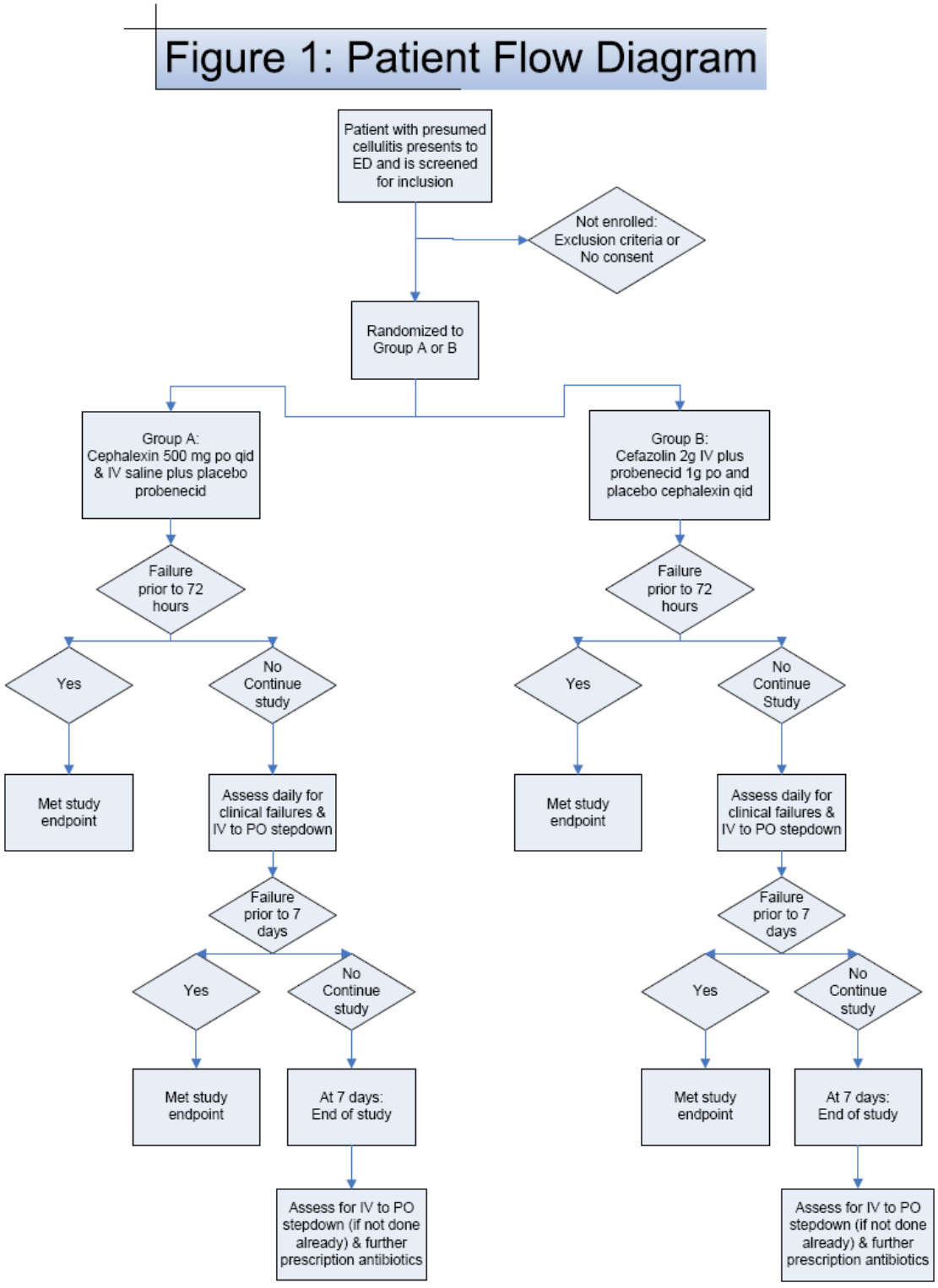
Figure 1: Patient Flow Diagram



Appendix I: Initial Visit Cefazolin/Probenecid vs Cephalexin Data Collection Form

Location of Presentation: __ KGH __ QEII HSC	
Study Number: Date of Initial Presentation: Age: Gender: Weight:	
Location of Cellulitis: __ Arm __ Leg __ Hand __ Foot Head/Neck Other	Vitals: temperature:_____ blood pressure:_____ heart rate:_____ resp rate:_____
Duration of cellulitis prior to ED visit: ___ weeks ___ days ___ hours	Symptoms: __ pain/tenderness (value out of 10____) __ fever __ swelling __ erythema __ localized warmth __ purulent drainage/discharge __ induration __ regional lymph node swelling/tenderness __ extension of redness __ new altered mental status
Antibiotic therapy in the past 7 days: __ Y __ N __ cephalexin __septra __clindamycin __other:_____	
Concomitant use of: __ topical antibiotics __ systemic steroids __ medications causing immunosuppression	
Known Diagnosis of: __ diabetes __ HIV __ haematological malignancy	Signs of Systemic Sepsis: __ temperature >38° C or <36° C __ heart rate > 90 beats/min __ respiratory rate > 20 breaths/min __ WBC <4,000 cells/mm³ or >12,000 cells/mm³ or >10% band forms
IV drug user: __ Y __ N	
Homeless: __ Y __ N	
Contact with the healthcare system in the past year: __ Y __ N	

Appendix II: Subsequent Visit Cefazolin/Probenecid vs Cephalexin Data Collection Form

<table>
<tr><td colspan="2">Study Number: Visit (circle day): 2 3 4 5 6 7</td></tr>
<tr><td>Vitals:

temp:_____ blood pressure:_____

heart rate:_____ resp rate:_____</td><td rowspan="2">Signs of Systemic Sepsis:

__ temperature >38° C or <36° C

__ heart rate > 90 beats/min

__ respiratory rate > 20 breaths/min

__ WBC <4,000 cells/mm³ or >12,000 cells/mm³ or >10% band forms</td></tr>
<tr><td>Symptoms:

__ pain/tenderness (value out of 10 ___)

__ fever

__ swelling

__ erythema

__ localized warmth

__ purulent drainage/discharge

__ induration

__ regional lymph node swelling/tenderness

__ extension of redness

__ new altered mental status</td></tr>
<tr><td colspan="2">Plan:

__ Continue study drug therapy

__ Step-down from IV to PO therapy

__ Admit to hospital

__ Change antibiotic therapy to:

__ clindamycin

__septra

__other:_____</td></tr>
</table>

Appendix III: Assessment at discharge and 7 days

<table>
<tr><td colspan="2">Complete AFTER success or failure has been concluded and BEFORE patient is unblinded:</td></tr>
<tr><td>Suspected Treatment Group:

Patient: __ oral cephalexin __ iv cefazolin plus probenecid

Physician: __ oral cephalexin __ iv cefazolin plus probenecid</td><td>Number of capsules left in patient vial:
_____</td></tr>
<tr><td colspan="2">If discharged from study PRIOR to day 7, telephone interview conducted on day 7:

__ not applicable

__ yes, contacted date/time:_____

If yes, does the patient have any:

__ visits to a physician since discharge? if so why:_____

__ visits to an ED since discharge? If so why:_____

__ signs or symptoms of cellulitis present?

__ pain or tenderness __ fever __redness __ localized warmth

__drainage __ swelling/ tenderness around infection

__extension of redness __ Other:_____</td></tr>
<tr><td colspan="2">Further prescription written for patient on day 7?

__ N __ Y If Yes: __Cephalexin __ Clindamycin __Septra

__ Other:_____

Why antibiotic given?

__ inadequate response __abscess formation

__ MRSA coverage __ Other:_____</td></tr>
</table>

Appendix IV: Patient chart information sheet for return visits

Capital Health Interior Health

Date of Enrolment: _____

TRIAL NAME: **Intravenous cefazolin plus oral probenecid vs. oral cephalexin for the treatment of cellulitis: a randomized controlled trial**

SUMMARY: It has been determined that this patient has cellulitis. As a participant in this trial, this patient is taking:

Cephalexin 500 mg 4 times daily
OR
Cefazolin 2 g IV daily plus Probenecid 1 g PO

PURPOSE: The purpose of this study is to determine how well *cephalexin* works to treat cellulitis compared to *cefazolin* and *probenecid*. Currently, the choice of which drug to use is left up to the physician and usually depends on past experience. The results of this study may be able to provide physicians with scientific evidence to guide their decision.

PROCEDURES:

	Initial Visit	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	End of Study
Background Information Collected	**X**							
Physician Assessment	**X**	**X**	**X**	**~**	**~**	**~**	**~**	
Patient Receives IV Treatment	**X**	**X**	**X**	**~**	**~**	**~**	**~**	
Patient Receives Oral Treatment 4 times a day	**X**	**X**	**X**	**~**	**~**	**~**	**~**	
End of Study Survey (One Question)								**X**

POSSIBLE DRUG THERAPY:

Group	Drug Therapy	Placebo
A	Cephalexin 500 mg 4 times a day	placebo probenecid capsule plus IV saline once daily
B	Probenecid 1 g PO plus Cefazolin 2 g IV once daily	placebo cephalexin capsules 4 times a day

If you have any questions or concerns regarding the participation of this patient in this trial.
For **KGH please call Dr. Dawn Dalen at 250-212-4452**
For **QEII HSC please call Dr. Peter Zed at 902-473-2967**
A signed copy of the patient's consent can be found in the patient's medical record.

Appendix IV: Consent Form (Please refer to attached consent forms)