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Cellulitis in the Emergency Department: Developing and Testing Objective Outcome Measures

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Thesis submitted to the School of Graduate Studies and Research, in partial fulfillment of the requirements for the M.Sc. degree in Epidemiology

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Abstract

Introduction: The treatment of cellulitis with intravenous antibiotics administered in Emergency Departments is a new phenomenon with significant inter-physician variation. A clinical trial will address many of the questions surrounding this practice. Previous trials have been flawed because of the absence of a validated objective outcome measure.

Methods: Eligible patients with cellulitis were prospectively recruited for an observational cohort study and underwent daily measurements of their infection. These measurements were evaluated for their feasibility, inter-rater reliability and criterion validity (compared with the primary outcome of treatment failure versus clinical response: a classification based on physician treatment decisions)

Results: Only the infection size and change in size over time performed well, obtaining statistical significance in all domains.

Conclusions: The change in size of infection over time is a valid and reliable reflection of clinical decisions for patients with cellulitis, and should be used as the primary outcome for clinical trials of cellulitis therapy.

1. INTRODUCTION

1.1 Presenting the Problem and Goals of the Thesis

1.1.1 Statement of the Problem

Emergency Departments across the country have over the last decade experienced a shift in the philosophy of patient care, becoming increasingly involved in the assessment and primary management of conditions that were previously treated only in hospital. One of the examples of this phenomenon is the approach to patients with skin and soft tissue infections. These patients are increasingly being treated as outpatients with intravenous therapy administered daily or several times daily through the Emergency Department, rather than being admitted to hospital. The practice of administering intravenous antibiotics to ambulatory patients outside of the hospital environment has been previously referred to as 'outpatient parenteral antibiotic therapy'.¹

1.1.2 Formal Documentation of Emergency Department-Based Intravenous Therapy

The shift from inpatient care to Emergency Department-based outpatient antibiotic therapy for patients with cellulitis has not yet been well documented in the published medical literature. However there are increasing formal and informal reports suggesting that this practice is widespread, at least in Canadian Emergency Departments. In 1996, a paper from St. Paul's Emergency Department in Vancouver compared the effectiveness of two different intravenous antibiotic regimens, administered once daily in the Emergency Department, for the treatment of cellulitis with and without associated abscesses.² A 1999 review of five Edmonton hospitals over a one-month period identified 321 patients treated with intravenous antibiotics as outpatients, 160 of whom were reported to have a skin or soft tissue infection.³ An abstract presented at a

Canadian Emergency Medicine conference in 1999 documented considerable variation in the choice of intravenous treatment of cellulitis patients among physicians in five urban Emergency Departments.⁴ Another abstract from a 2001 Canadian Emergency Medicine conference examined the outcomes 346 patients whose skin infections were treated with Emergency Department-based intravenous antibiotic therapy over a one-year period.⁵ Clearly this practice is common in Canada, and of some significant interest to practising Emergency Physicians.

1.1.3 Overview of Thesis Objectives

The primary purpose of this thesis is to set the stage for the conduct of a major randomized controlled trial of cellulitis treatment by addressing the following five objectives. The first is to obtain a description of the patient population with cellulitis (demographic features, co-morbidities and the clinical manifestations of cellulitis) in one academic centre. The next goal is to evaluate the level of agreement of physicians in their evaluation of the characteristics and severity of the infections they treat. The third goal is to compare a number of measurements of the clinical manifestations of cellulitis and to evaluate their usefulness as clinical outcome measures. These measurements will be evaluated for their ability to define the expected course of patients whose cellulitis is successfully treated and to identify deviations from this course that would constitute treatment failure. The fourth goal is to examine the clinical features of patients diagnosed with cellulitis that correlate with the physician impression of severity. The final goal is to examine features of patients at the onset of treatment that are associated with (and may therefore predict) treatment failure. Once these steps have been accomplished, the stage

will be set for a clinical trial comparing oral and intravenous therapy for patients with cellulitis presenting to the Emergency Department.

1.2 Defining the Spectrum of Skin and Soft Tissue Infection

1.2.1 What is cellulitis?

Skin and soft tissue infections comprise a large group of heterogeneous infectious processes caused by Group A beta-hemolytic Streptococci, or by *Staphylococcus aureus*. In order to understand the literature published on this topic, a careful description of the relevant clinical syndromes encompassed by the term 'cellulitis' is required. The term 'cellulitis' has been defined as "a general descriptive term suggesting infection and indicating the warmth, erythema and induration of skin and/or subcutaneous tissues, with or without pain."⁶ It is nearly always caused by Gram positive organisms: Group A beta-hemolytic Streptococci, (usually *Streptococcus pyogenes*) or by *Staphylococcus aureus*.^{7,8} Cellulitis may occur spontaneously and involve infection of the skin, subcutaneous fat and lymphatics, or it may develop in response to some pre-existing trauma, in which case it is defined as a *wound infection*. Wound infections should have greater than one centimeter of induration around the wound margin and some evidence of suppuration in order to be defined as such.⁹ The term 'erysipelas' refers to a specific clinical syndrome consisting of the acute onset of pain followed in a matter of hours by warmth and swelling in a well-demarcated plaque of indurated, erythematous skin.⁶⁻⁸ Cellulitis, wound infections and erysipelas, despite being separate and distinct infectious entities, are frequently grouped under the 'catch-all' heading of cellulitis since they are all treated

with the same types of antibiotics: anti-staphylococcal penicillins, cephalosporins and more recently fluoroquinolones and macrolides.^{6,7,8}

1.2.2 What is an Abscess?

Cellulitis will ordinarily respond to antibiotic administration alone. Occasionally, soft tissue infections will experience the enzymatic process that results in liquefaction, necrosis and localized pus formation – the development of a soft tissue abscess. Simple abscesses will frequently resolve with incision and drainage of the pus cavity, but occasionally also require antibiotic therapy.⁹⁻¹¹ Consequently, abscesses with noticeable surrounding areas of erythema or systemic symptoms of infections have been eligible for inclusion in cellulitis trials following incision and drainage.”

1.2.3 Necrotizing Fasciitis: A Life-Threatening Soft Tissue Infection

“*Necrotizing fasciitis*” is a term used for any infectious process, which extends beyond the skin and subcutaneous fat into the fascial planes below. A frequently used and well publicized layman’s term for this devastating infectious process is ‘flesh-eating disease.’ This life-threatening infection typically presents with severe pain, marked systemic signs of infection and inflammation and eventually necrosis of the overlying skin with septic shock and circulatory collapse.^{6,8,12} Although it is often caused by the same organism as uncomplicated cellulitis (*Streptococcus pyogenes*), this catastrophic infection represents the most extreme end of the spectrum of skin and soft tissue infections. The approach to treatment differs from simple cellulitis in that early and aggressive surgical debridement of infected tissue (and/or amputation) is extremely

important. It occurs uncommonly in any one clinical setting, and patients suspected of harbouring necrotizing fasciitis are not part of the cohort addressed in this thesis.

1.2.4 Other Types of Soft Tissue Infections

Also included under the general heading of skin and soft tissue infections are human and animal bite wounds and superinfection of pre-existing ulcers (decubitus ulcers and diabetic foot ulcers).⁸ These infections are caused by a different collection of organisms and consequently the antibiotic therapy and ancillary investigations differ from those generally employed in treating cellulitis. These infections should be classified as 'complicated' skin and soft tissue infections and studied separately from the spontaneously arising or post-traumatic skin and soft tissue infections discussed above (or 'simple' cellulitis). Specific infections of digits (paronychia, felons and tenosynovitis) and superficial infections of epidermal tissue such as impetigo are also not part of the relevant study population, as the management of these infections is limited to incision and drainage (the former) and topical antibiotic creams (the latter).

1.3 Examining the Issues Surrounding Outpatient Intravenous Antibiotic Therapy

1.3.1 Evolution of Outpatient Parenteral Antibiotic Therapy

Reports of home or outpatient intravenous medication administration have been published increasingly since the 1970's.¹³ The evolution of better delivery systems, more advanced methods of intravenous access, longer acting parenteral antibiotics, improved infrastructure such as home care programs and home intravenous programs means that home intravenous antibiotic therapy is a well accepted entity for clinical medicine in the new millennium. In fact, it has been estimated that nearly a quarter of a

million Americans are treated with home based outpatient parenteral antibiotic therapy every year.¹³ and that trend is certainly reflected in the Canadian health care system. There have been numerous publications documenting the safety, efficacy and cost savings associated with home administration of intravenous antibiotics for skin and soft tissue infections, including cellulitis.^{1,14,15,16-18} However, none of these studies have involved patients randomized to home or inpatient care and consequently a recent review using strength of recommendation grades classifies outpatient parenteral antibiotic therapy for cellulitis as Grade “B” (moderate evidence to support a recommendation for use).¹ Additionally, all the studies have utilized a regimen of ‘convalescent’ outpatient parenteral antibiotic therapy where patients are stabilized in hospital and then converted to outpatient parenteral antibiotic therapy for the remainder of the intravenous antibiotic treatment.^{1,14-18} This is clearly a different scenario than the current trend of initiating and monitoring outpatient parenteral antibiotic therapy through the Emergency Department without first admitting the patient and ensuring an adequate treatment response. As experience with outpatient parenteral antibiotic therapy grows, it has become evident that the site of administration is varied: patients receive outpatient parenteral antibiotic therapy anywhere from home to outpatient clinics, doctor’s offices and Emergency Departments. The Emergency Department with its 24-hour operation schedule and constant physician availability makes it an ideal forum for intermittent parenteral therapy and reassessment of clinical condition. A daily physician assessment has the potential to reduce the number of days of therapy (most home-based outpatient parenteral antibiotic therapy programs run antibiotics for a predetermined length of time followed by a physician assessment) and to rapidly identify complications requiring intervention and

treatment failure. But does Emergency Department-based outpatient parenteral antibiotic therapy for cellulitis truly represent good medical care, particularly when the home-based programs are well established and researched?

1.3.2 Problems with Emergency Department-Based Outpatient Parenteral Antibiotic Therapy

There are several problems with treating cellulitis using Emergency Department-based outpatient parenteral antibiotic therapy. Wide varieties of antibiotic choices, doses and dosing schedules combined with a lack of continuity within the Emergency Department (a different doctor with different treatment philosophies for each patient encounter) have made the treatment courses and visit schedules for these patients confusing and often frustrating for all involved. Even in Emergency Departments with standardized care pathways for these patients, variable opinion over what constitutes 'improvement,' when the intravenous regimen may be switched to an oral one and disagreement over who should be eligible simply adds to the confusion. Multiple visits to the Emergency Department by patients for the same problem (as occurs with an intravenous treatment regimen) are expensive to the health care system, and time consuming for both doctors and patients. Headlines about clogged Emergency Departments fill our newspapers, and advertising campaigns urge patients to see their family doctors or use telephone health advice lines rather than visit the Emergency Department. One wonders whether asking patients to return day after day to wait in line for Emergency Department-based outpatient parenteral antibiotic therapy benefits anyone in the system. In fact, a provocative abstract was presented at a recent Canadian Emergency Medicine conference which suggested that patients given a single dose of

intravenous antibiotics followed by a course of oral antibiotics actually had fewer treatment failures than those treated with Emergency Department-based outpatient parenteral antibiotic therapy.¹⁹

Additionally, there exists a belief that patient outcomes may be improved if soft tissue infections are treated initially with intravenous antibiotics. Since patients no longer need to be admitted to receive this, it has become very easy to initiate a course of intravenous treatment and ask patients to return to the Emergency Department for a recheck. Classification of “serious” and “mild” skin and soft tissue infections has been derived in review articles by identifying co-morbidities (such as diabetes and peripheral vascular disease) that predispose patients to more complex infections and physical exam features (such as fever, nausea, vomiting, and lymphangitis) which imply more serious infections with systemic involvement.^{6,7,12,14,20-22}

The presence of any of these co-morbidities and physical findings are assumed to predict a potentially poor outcome and used to justify the need for intravenous antibiotics and admission. But there is no evidence to support the assumption that patients with particular co-morbidities and physical exam findings have poor outcomes, or that they require intravenous therapy and/or admission in order to improve. Published opinions differ as to which characteristic or combination of characteristics is most important in making admission decisions. The situation is made murkier by the frequent failure to distinguish between the severity of a skin infection and the complexity of the infection. There is widespread use of undefined and ambiguous terms like ‘severe,’ ‘moderately-severe,’ ‘mild-moderate,’ ‘complicated’ and ‘uncomplicated’ among the guidelines for treatment and admission decisions.^{6,7,12,14,20,21,22}

1.3.3 Oral Antibiotics as an Alternative

Several infectious disease experts have recently published papers urging a return to oral antibiotic treatment for many common infectious diseases, including cellulitis.²³⁻²⁵ Currently available oral agents have excellent spectrums of activity and tissue penetration, and should be effective in treating the vast majority of skin and soft tissue infections seen in the Emergency Department. Comparisons of plasma levels between orally and intravenously administered antibiotics have shown equivalent concentrations, suggesting that oral and parenteral therapy should be equally efficacious (assuming good patient compliance).^{23,25} There are several potential disadvantages of intravenous antibiotic therapy including phlebitis, secondary infection from the catheter site and excess fluid administration. However, vague definitions of what exactly constitutes a mild or moderate infection and easy access to intravenous therapy may have created an environment where all but the most trivial infections are treated with intravenous antibiotics.

1.3.4 Questions Raised About Emergency Department-Based Outpatient Parenteral Antibiotic Therapy

In order to address some of these issues and properly evaluate the practice of Emergency Department-based outpatient parenteral antibiotic therapy, several questions come to mind. Which patients require hospital admission? (Despite the wide use of outpatient parenteral antibiotic therapy in all its locations, some patients with skin and soft tissue infections are still admitted to hospital for the duration of their treatment). Which infections need intravenous antibiotic therapy as opposed to oral therapy and what

criteria are used to define severity? And finally, are there well-defined clinical parameters for cure, improvement or treatment failure?

1.4 Literature Search

1.4.1 Literature Search Strategy

A literature review was performed to identify published work that would address these questions. Specific terms were entered into the “medical subject heading” fields of the OVID search software for the computer-based Medline Database, encompassing the years 1966-2000. These same terms were then searched under the “textword” fields (encompassing both the title and abstracts of articles in the Medline Database) in order to create an initial list of articles. The Cochrane Library was also searched using the same subject and textword headings. The abstracts from this list were manually reviewed and potentially relevant articles were retrieved. Any relevant secondary articles identified through the reference lists were also retrieved. Conference abstracts over the last 10 years for the major Canadian and US Emergency Medicine Research Meetings were hand searched and any abstracts on cellulitis were reviewed. Content experts in Infectious Diseases and Emergency Medicine at Queen’s University and the University of Ottawa were also consulted to ensure that no important publications were overlooked.

The specific subject terms used in the search were: “skin diseases, infectious,” “soft tissue infections,” and “cellulitis.” A filter was used to limit the search to clinical trials. Three hundred eighteen potentially relevant articles were screened, and 98 articles were obtained for review. The search was repeated combining the results with the subject heading “emergency medical services” and the textwords “emergency,” “emergency

medicine” and “emergency department.” Another 53 articles were identified and screened from this search, and 7 were obtained for review. The search was repeated one further time to examine review articles and overviews. A filter was used to limit the results to English language publications and studying only adult humans. Of potential 816 review articles, 91 were felt to be possibly relevant, and were obtained for review. These searches resulted in a collection of 196 articles, summarizing current opinion on the etiology, severity and treatment of cellulitis, the work previously published regarding Emergency Department patients with cellulitis and a collection of the published Medline-cited clinical trials of cellulitis therapy.

1.5 Criteria Used to Define Severity in Clinical Trials

1.5.1 Recommendations for Conducting Cellulitis Trials

The US Food and Drug Administration’s Center for Drug Evaluation and Research published a document in 1992 on their website entitled “Points to Consider: Clinical Development and Labeling of Anti-Infective Drug Products.”²⁶ The aim of this document is to provide guidance to individuals and agencies developing anti-infective drug trials. One of the early recommendations of the authors is that trial protocols should “carefully distinguish ... between the severity of a disease entity (mild, moderate and severe) and the complexity of a disease entity (complicated and uncomplicated).”²⁶ Later, in the section on skin and soft tissue diseases, the authors recommend that “protocols used to study an investigative product for treatment of these infections should have very clear inclusion, exclusion, evaluability criteria and outcome definitions, as the primary effectiveness parameter for this infection should be clinical outcome.”²⁶

Also in 1992, a set of guidelines was published in the journal *Clinical Infectious Disease* regarding the conduction of clinical trials for patients with skin and soft tissue infections.⁶ Again it was felt to be fundamental to the validity of these trials to include clear and objective inclusion and exclusion criteria and objective measures of clinical outcome.

1.5.2 Published Criteria for Defining Severity

Despite these exhortations, published clinical trials of antibiotic therapy for cellulitis lack clear and objective criteria for clarifying the severity of infection in eligible patients. A 1992 review of three clinical trials evaluating the antibiotic cefprozil commented on the patients enrolled as having “one or more clinical signs and symptoms... consistent with a mild-to-moderate cutaneous infection for which treatment with an oral cephalosporin... or oral erythromycin was appropriate.”²⁷ These three trials excluded all patients who were felt to have “a severe infection that might require the use of parental antibiotics.”²⁷ These vague definitions are standard in cellulitis research, with subsequent trials taking their cue from the previous work. Thus trials of oral antibiotics are conducted on patients with ‘mild’ or ‘mild to moderate’ infections, while trials of intravenous antibiotics are conducted using patients admitted to hospital with ‘moderate to severe’ infections.²⁸⁻⁶¹

1.5.3 Using the Presence of Co-Morbidities to Define Severity

As mentioned previously, the traditional approach to the assessment of cellulitis has been to identify and document co-morbidities that are felt to predispose patients to more severe illness. Several textbooks recommend that admission decisions be based in part on the presence of one or more of these co-morbidities.⁶²⁻⁶⁵ The problem with this

approach, as mentioned previously, is that there is no evidence supporting the assumption that patients with particular coexistent medical problems have more severe or more complicated episodes of cellulitis, in the absence of other indicators of severity.

1.5.4 Cellulitis in Diabetic Patients

Diercks et al. in an abstract examining “appropriate admission” in 443 Emergency Department patients with cellulitis found that 11.5% were reported as having diabetes. This proportion increased to 17% in patients admitted for treatment.⁶⁶ Two other reviews of admitted patients found that 14% and 20% of patients, respectively, reported a history of diabetes.^{61,67} Another abstract examining predictors of admission for treatment of cellulitis found on multivariate analysis that the presence of diabetes was associated with admission to hospital (adjusted odds ratio 2.1).⁶⁸ The high proportion of diabetic patients in these studies would appear to support the assumption that patients with diabetes are more likely to develop skin infections than their non-diabetic cohort. It also seems that diabetic patients are more likely to be admitted to hospital for treatment.

An extension of this premise is the question of whether patients with skin infections are more likely to have undiagnosed diabetes than a similar age-matched cohort. A retrospective review published in 1996 found a history of diabetes in 9.8% of 500 admitted patients with cellulitis, but a further 21% of 265 non-diabetic patients screened while in hospital had abnormal glucose tolerance tests.⁶⁹ However, a prospective study published in 1993 found that Emergency Department screening did not identify significantly more undiagnosed diabetic patients in the group with skin infections than in a matched control group.⁷⁰

1.5.5 Problems with Assessing the Prevalence of Co-Existent Illness

There are many problems with the accuracy of assessing the presence of co-morbidities, particularly in retrospective studies. For example, the prevalence of peripheral vascular disease varies widely from study to study. One retrospective review of admitted patients reported that 39% of its population had “arterial disease,”⁶ while a different study reported only 6% with peripheral vascular disease.⁷ There are at least two possible explanations for this discrepancy, the first being the retrospective nature of the studies and the subsequent dependency on documentation (or lack thereof) of the condition of interest in the patient’s medical record.

Another explanation is the difficulty of precisely defining ‘peripheral vascular disease.’ Should investigators label patients as having peripheral vascular disease only if they have had investigations confirming impaired peripheral arterial circulation? Or should they also identify patients who report symptoms consistent with impaired circulation (such as claudication and ischemic pain)? Should these studies label patients as ‘positive’ for peripheral vascular disease if they exhibit physical findings suggestive of chronic peripheral ischemia but have never undergone confirmatory tests or experienced any symptoms? The difficulty of precisely defining the presence of these conditions makes it nearly impossible to draw conclusions about their true prevalence amongst patients with skin infections, let alone the effect of the disease on the outcome of a skin infection. It is certainly plausible that many of these conditions render the hosts more susceptible to skin and soft tissue infections. The unanswered question remains whether patients with co-morbidities are more likely than ‘healthy’ patients to fail standard

treatment for skin infections. If this were the case, it would then justify the need for more aggressive treatment.

1.5.6 Using Size of Infection to Define Severity

If the presence or absence of co-existent illness is not a useful marker for severity, perhaps an objective indicator like size of infection could be used. However, only one of the published clinical trials of cellulitis treatment measured and reported the size of infection at the time of enrollment.⁷² This oral antibiotic trial conducted in Great Britain reported the area of redness in the two treatment groups at the beginning of an outpatient treatment course. The mean area of redness (and standard error) in the first group was 74.4cm^2 (21.2) and 51.5cm^2 (9.8) in the second. All 96 patients in the trial recovered while taking oral antibiotics, and none required hospital admission or intravenous antibiotics. The only other published reference to the size of infection as a characteristic of severity was in an abstract published in the journal *Academic Emergency Medicine*. The authors of this abstract compared clinical and laboratory variables in patients with extremity cellulitis who were admitted to hospital with those who were discharged.⁶⁶ The mean area (and standard error) of patients requiring admission was 169.7cm^2 (206.3) while the mean area of patients treated as outpatients was 58.7cm^2 (87.1).

These two studies suggest that the size of the infected area is an important indicator of infection severity, and may be one of the features influencing physician decisions about hospital admission and or intravenous therapy.^{66,72} However, apart from these two studies, all the trials identified in the literature review were comparing antibiotics rather than attempting to evaluate the need for admission and intravenous therapy, and none of these trials provided any guidance for severity assessment other than

physician judgment. In the large collection of trials comparing different antibiotics, the criteria for parenteral treatment and/or admission for patients with cellulitis remain undefined.

1.6 Defining Treatment Failure and Clinical Outcomes

1.6.1 What Outcome Measures Have Been Used?

The same problem of vague, non-standardized definitions occurs in the evaluation of patient outcomes and in the definition of treatment failure. The first problem seen in many of the trials is the reporting of 'bacteriologic cure' – the eradication of any bacteria grown from the infection site. This step is felt to be important in any trials of anti-infective agents, mainly to ensure that the infecting organisms are sensitive to the treatment drugs. However, many trials have simply dropped from further evaluation any patient in whom cultures failed to grow a causative organism.^{28,29,33,37,38,42,51,54,57,60,73-75} Since patients with cellulitis have a very low rate of positive skin and blood cultures,^{76,77} this step eliminates many eligible patients. This practice saddles the trials with a significant selection bias, since patients with positive cultures are very likely different from patients with negative cultures. Again, the specific advice from the US Food and Drug Administration's Center for Drug Evaluation and Research was: "*the primary effectiveness parameter for this infection should be clinical outcome.*"²⁶

There are also some significant problems in the evaluation of clinical outcomes in the cellulitis trials. In examining these trials, the most striking feature has been the absence of objective clinical parameters for improvement. Most clinical outcome measures are reported in a graded fashion based on investigator assessment of clinical

response, from 'cure' and 'incomplete cure' to 'treatment failure.' There is very little objective guidance for the duration of time when improvement would be expected, a large grey area encompassed by the 'improvement' category and very few attempts to define treatment failure in any way other than "lack of resolution of the infection."² In other words, the patients appeared to be labelled as 'improved' when the clinicians looking after them decided that they were improved, as evidenced by discharge from hospital, a switch to oral agents after intravenous therapy, or withdrawal of antibiotics altogether.

While this approach may have some validity when the same investigator is seeing the same patient day after day, it is certainly not feasible in the Emergency Department where changing caregivers are inherent to the system. This approach is also clearly inadequate when conducting any kind of multi-center investigation, since there are no clear and objective standards that are reproducible in different locations. How do we decide when someone is getting 'better' from cellulitis? The absence of any kind of objective scoring system and poor or absent definitions of what constitutes treatment failure or 'getting worse' make these trials impossible to reproduce and leads to problems in the design of the future studies.

1.6.2 Using Time to Improvement to Define Treatment Failure

One well-established cellulitis researcher outlined a time frame for treatment failure in two published clinical trials.^{42,78} In a 1987 study, treatment failure in outpatients with mild infection was defined as "persistence of local signs of infection, fever, or leukocytosis after 3 or more days of therapy."⁷⁸ This same time frame was also used to evaluate improvement in a recent abstract evaluating the effectiveness of oral

antibiotic therapy after a single intravenous dose in the Emergency Department.¹⁹ A subsequent study on inpatients with more significant infections used a “lack of response to therapy after ≥ 48 hours of treatment” as the definition of treatment failure.⁴²

There is little information regarding the expected time to improvement for patients being treated for cellulitis in review articles or textbooks. Any mention of time frames for improvement seems to be restricted to unreferenced opinion - statements that patients receiving appropriate antimicrobial therapy (oral or parenteral) should demonstrate improvement within 24 to 48 hours.^{62 20} In contrast, a retrospective review of 118 patients hospitalized with lower limb cellulitis found that in the 86 patients with documentation of improvement, it took five days for 80 (94%) to have an improvement recorded in the chart. The mean duration of stay in hospital for “simple cellulitis was 7.5 days, corresponding closely to the average duration of intravenous therapy.”¹⁴ These data suggest that the expected time frame to improvement in hospitalized patients may be somewhat longer than 24 to 48 hours, although the retrospective nature of the study prevent any conclusions from being drawn.

1.6.3 Using Surgical Intervention to Define Treatment Failure

There appears also to be some confusion regarding patients who require subsequent surgical intervention. One trial of two intravenous antibiotic regimens included patients with surgical cures in the overall ‘cure’ category.⁴⁵ With 6 amputations and 14 incision and drainage procedures in the 20 ‘cured’ patients, it is a huge leap of faith to credit the antibiotic therapy as being responsible for the cure. One other study simply documented the number of incision and drainage procedures on each arm of the

trial as relevant outcomes, and compared the numbers to ensure that the groups were balanced.²

The 1992 Clinical Infectious Diseases guidelines state that “if a surgical procedure...is undertaken >48 hours after treatment is initiated, drug therapy should be considered to have failed.”⁶ These guidelines were derived through a consensus of expert opinion. It seems reasonable to present this criterion as one component of a definition of treatment failure for patients with cellulitis.

1.6.4 Using Change in Infection Size as a Clinical Outcome Measure

A possible outcome indicator is the ratio of infection diameters before and after therapy. This assumes that halving the size of a large infection is equivalent to halving the size of a small one. It also assumes, if time under treatment is incorporated (reduction in size per day), that progress is linear. One recent study used this ratio in the comparison of two groups of Emergency Department patients receiving intravenous antibiotics for cellulitis.⁷ The average ratio of the size of infection on the first treatment day to the size of infection on the last day was found to be less than 1 in both treatment groups. This suggests, as expected, that the size of infection decreased as the infection began to heal. The ratios are not as small as might be expected, though – the mean ratio in the first group was 0.8 (SD 0.5) and 0.7 (SD 0.4) in the second, with medians of 1.0 and 0.8 respectively. This suggests that some patients being treated actually had an increase in size. This finding may be partially explained by the inclusion of patients who subsequently required an incision and drainage (23% in one group and 35% in the other).

The authors of this paper are to be commended for their attempt to create a transparent and reproducible outcome. However, the study methodology has significant

problems. Firstly, the last day of treatment for the study patients was not determined by a physician decision but instead by the patient failing to return – are these patients really all better or have they instead gone elsewhere for treatment? None of patients were contacted after their final visit to the Emergency Department to verify that they continued to improve. A second problem exists with the timing of the comparison of first and last day's size. The average duration of intravenous antibiotic therapy in both groups was between 2 and 3 days. There was a great deal of variability, however - more than 25% of the study patients received just 1 day of treatment while another 25% required more than 4 days. The ratio of infection size at first presentation to size on the last day, then, compares patients with extended courses to patients with very brief courses of antibiotics. There was no attempt to standardize, and compare the change in size at the same times between groups. This would have provided a better reflection of the clinical course. Finally, the study hospital is an inner city hospital that serves a transient population with a high proportion of intravenous drug users, and soft tissue abscesses, so the findings in this population may not be applicable to other centers.²

1.6.5 Using Several Objective Measurements as Outcome Measures

One other study used concrete outcome measures to compare two groups of outpatients and their response to two different oral antibiotics.⁷² Measurements of cellulitis size, redness and patient pain were taken on the first day of treatment and at the end of a 14-day course and compared between groups. The mean size of infection in the two study groups (and standard deviation) was 74.4cm² (21.2) and 51.5cm² (9.8) on the first day and 27.0cm² (13.4) and 12.4cm² (5.5) on the 14th and final day. Although the authors did not employ the ratio variable (size of infection on the first day: size on the

last day) used in the Brown study.² this can be calculated as 0.36 and 0.24 in the two groups.

Study patients graded their pain as “improved,” “same” or “worse” every two days during the study, and at the same visit the 16 treating physicians rated the intensity of redness on a 10cm visual analogue scale (0 = “skin normal colour, no inflammation” and 10 = “skin very red and inflamed”). Approximately 25% of patients in both study groups reported an improvement in their pain at day 2 while slightly more than half were improved at day 4. Interestingly, 5% of patients in the first group and 15% in the second reported no change in their pain at the end of the two-week antibiotic course. The authors report that “the pain associated with cellulitis improved significantly with both treatment after five days and that the improvement was maintained,” although the numerical data for this parameter were not presented.²² The mean redness score (and standard deviation) in the two groups on the first day was 7.8cm (0.2) and 7.7cm (0.3) compared to the 14th day scores of 1.8cm (0.3) and 0.9cm (0.2).

These authors have made a valiant attempt to standardize the assessment of patients in their multi-center trial. Unfortunately there are some problems with this study which need to be identified. Firstly, the patient population is not well defined: the reader is told that these patients were outpatients being treated by British general practitioners with oral antibiotics but there is no demographic information presented beyond age, sex, height and weight. Important information is missing from the published paper: the presence of co-morbidities such as diabetes and peripheral vascular disease and the frequency of presenting symptoms such as fever, nausea and lymphangitis. Six of the 96 patients were withdrawn, some of them for “lack of efficacy,” and their data appears to

have been excluded from analysis.⁷² A significant number of patients (17% and 31%) in the two groups required more antibiotics after the 14-day study course. The data from these patients is blended with the data from the patients who were cured with the first course of antibiotics.

There was no clear definition of treatment failure at the start of the study, so it becomes difficult to extrapolate what a 'successful' course would be in these patients. For example, is the residual pain and redness documented at the end of the antibiotic treatment what we would expect in a 'cured' patient? Or was this finding strictly limited to patients who were subsequently prescribed more antibiotics? Finally, there is no record of any attempt to assess the interobserver reliability of these measurements. Did the 16 physicians all agree in their assessments of the severity of the infection? Is the VAS scale of redness a valid and reproducible measurement of infection severity?

1.6.6 Summary of the Review of Outcome Measures Used in Published Clinical Trials

After an extensive review of the published literature, it becomes apparent that there are significant gaps in our approach to cellulitis research. There are no clear guidelines for the assessment of cellulitis severity, little understanding of the natural course of cellulitis as it improves with treatment and only a few limited attempts to define treatment failure and create concrete and reproducible clinical outcome measures.

1.7 Approach to Developing an Outcome Measure

1.7.1 Features of a Good Outcome Measure

Clinical outcomes are the fundamental tools with which we measure the effectiveness of a therapeutic intervention. In diseases with a high mortality rate and a

well-defined course, the outcomes may be intuitive and easy to track. When evaluating cellulitis, however, mortality has been almost unheard of since the introduction of antibiotic therapy and the course is anything but well defined. Tugwell and Bombardier have listed the six essential features of a good outcome for use in clinical trials as credibility, comprehensiveness, sensitivity, accuracy, biological sense and feasibility.⁷⁹ The term 'accuracy' in this paper reflects the criterion validity; however, a discussion of the development of an outcome measure would be incomplete without mentioning the reliability or reproducibility of the measure (another key component of accuracy). A useful endpoint for a cellulitis trial, then, would be relevant and acceptable to both physicians and patients, capture the important manifestations of the illness, represent the clinical response to antibiotic therapy, be easy to evaluate and demonstrate good interobserver reliability. How does one go about identifying and testing such an outcome?

1.7.2 Satisfying the Criteria of Biologic Sense and Comprehensiveness

The first step in developing this outcome is to examine all of the clinical manifestations of skin infections and select measurements that reflect these manifestations. This theoretical construct of the features of a skin infection may be thought of as a conceptual framework. Documenting and developing measurements to represent all of these features will satisfy the criteria of comprehensiveness and biologic sense. This first step may be compared with the process of *item selection* in the development of questionnaires used to measure disease-specific quality of life.⁸⁰

1.7.3 Making Biologic Sense: Manifestations of Skin Infections

The objective measurements we have chosen to study follow two well-recognized conceptual frameworks of the clinical manifestations of skin infections. The first model captures the physical manifestations of all skin infections: visible redness, warmth and pain at the infection site.⁶²⁻⁶⁵ We would expect that as patients began to improve, and report improvement, that the clinical manifestations of the infection would diminish. Thus the measurements (intensity of redness, size of redness, temperature difference between infected and uninfected skin and pain) will decrease in patients who are improving, while they will enlarge (or at least, not shrink) in those patients who are failing treatment. Thus, assuming that the measurements are the same in both groups at the onset of treatment, we should see a significant difference between the treatment successes and the failures as the clinical course is defined. Additionally, we should see a correlation between patient reports of improvement and an observed improvement in the infection.

1.7.4 Making Biologic Sense: Manifestations of Local or Systemic Spread

The second model encompasses the features of local or systemic spread of an infection: the presence of local lymphadenopathy or lymphangitis, fever, and systemic symptoms such as nausea vomiting and myalgias.⁶²⁻⁶⁵ This model, however, is fundamentally different from the first model in that not all patients with skin infections will show evidence of any local or systemic spread of their infection. So this model and these particular measurements can only be tested in a smaller subset of the population of patients with skin infections – those who have, or develop during the study, evidence of infection spread. We would expect that patients who are responding to treatment will

exhibit resolution of these signs of local or systemic spread (they will disappear) while those who are failing treatment will show either a lack of resolution or will develop them (as a new finding) after the treatment is initiated.

1.7.5 The Process of Refining the Selected Measurements: Satisfying the Criteria of Criterion Validity and Feasibility

An outcome measure in a clinical trial of cellulitis must function as an evaluative instrument, and be able to distinguish between patient who are improving and those who are not. An evaluative instrument measures a clinical response over time (or lack thereof), and ideally should have the following properties: it should be sensitive to clinical change (sensitivity), agree with other instruments measuring the same response (criterion validity), and match hypothesized predictions of the investigators (construct validity).^{79,81,82} Since there is clearly no gold standard or reference criterion in the study of cellulitis, the process of validation must follow the model of construct validation. Using this model, the hypotheses described above regarding the performance of the measurements are tested.

The process of evaluation will also demonstrate unforeseen difficulties in gathering and recording the some of the measurements: the unwieldy measurements may also then be eliminated. It should then be possible to reduce the number of measurements by identifying one sign or a small number of signs that most accurately follow an identifiable sequence indicating stages of resolution of the infection. This second step may be compared with the process of *item reduction* in the development of questionnaires used to measure disease-specific quality of life.⁸⁰

1.7.6 Examining the Reliability of the Measurements

Examining the reliability of the measurements is another critical component of the evaluation of their usefulness as clinical tools. In addition to closely reflecting the true clinical state (criterion validity), the reliability or reproducibility of the measurements must be examined. The component of reliability most important for a clinical trial is the interobserver agreement. Measurements with poor interobserver agreement will not be useful as outcome measures in a multi-centre or even a single center Emergency Department trial.

1.7.7 Further Refinements in the Outcome Measures: Satisfying the Criteria of Sensitivity and Credibility

Once the number and scope of the measurements have been reduced, further assessment should concentrate on the sensitivity to change and the clinical credibility of the remaining measurements. Useful outcome measures should be able to reflect very small but relevant changes in the health status of patients. The concept of a 'minimal clinically important difference' has been used to translate statistically significant differences into clinically relevant differences.⁸³ This is frequently done by comparing differences in a specific outcome on a continuous scale with ratings for the same outcome on a descriptive (usually categorical) scale, or by obtaining an expert consensus.⁸⁴⁻⁸⁶ Once a minimal clinically significant difference has been identified, we can then use this change in measurement as a primary outcome measure.

The credibility of an outcome measure in cellulitis should be evaluated by assessing physician willingness to act on clinically relevant changes. For example, a

definition of treatment failure developed using the criteria above should then be tested in a clinical setting to ensure that there is physician agreement.

1.8 Summary

The treatment of cellulitis and related infections with intravenous antibiotics administered in Canadian Emergency Departments is a relatively new phenomenon. There is considerable variation in the type, dose and frequency of antibiotic administration, and no evidence regarding which patients require intravenous therapy or admission. Previously published clinical trials have been flawed primarily because of the absence of a validated objective outcome measure, and poorly defined or non-existent definitions of treatment failure.

A clinical trial randomizing Emergency Department patients either to one dose of intravenous therapy followed by oral therapy or to daily Emergency Department-based intravenous therapy would address many of these issues. However, the development and preliminary validation of objective outcome measures must precede any clinical trial. Objective measurements of cellulitis should be assessed in seven key areas: the ability to capture the manifestations of cellulitis, make biologic sense, exhibit sensitivity to change, criterion validity, credibility with clinicians, inter-observer reliability and feasibility.

2. Objectives:

Study objectives are the following:

- 1) To obtain a *description of the population of patients* presenting to Emergency Departments with skin and soft tissue infections, specifically evaluating patient demographics, infection characteristics and outcomes (number of complications, days of treatment required and numbers of admissions). This will allow a sample size calculation for a clinical trial of cellulitis treatment.
- 2) To *evaluate the level of agreement among ED physicians* in their assessment of the clinical features and characteristics of cellulitis. Any measurement with poor interphysician agreement should not be used in the evaluation of cellulitis.
- 3) To *define the normal clinical course* of cellulitis, and to identify deviations from this course that constitute treatment failure, using objective and reproducible measurements. Several objective measurements will be evaluated for their ability to track progress over time, and to reflect the clinical impression of severity.
- 4) To examine the clinical *characteristics which determine the severity* of an episode of cellulitis. (The type and route of antibiotic selected and the location of administration of that antibiotic were used to define severity). Once the characteristics of severity have been defined, the patient population for a clinical trial can be more precisely identified.
- 5) To identify any *clinical features which predict treatment failure* at the first Emergency Department visit. Patients with clinical features highly associated

with treatment failure should be excluded from randomization in a future clinical trial (it is unethical to randomize patients to a treatment that will not be beneficial).

3. Methods (Chart Review)

3.1 Design and Setting

This was a retrospective chart review, conducted at a single centre (Kingston, Ontario) with two hospital sites and Emergency Departments: Kingston General Hospital (full service inpatient care) and Hotel Dieu Hospital (outpatient day hospital). These hospital sites comprise the tertiary care teaching hospitals for the Emergency Medicine Program at Queen's University. The hospitals serve a regional population of 120,000 people. Kingston General Hospital had 50,275 Emergency Department visits in 1998 and an admission rate of 17.6%. Hotel Dieu Hospital is a 14-hour urgent care facility with 35,942 visits in 1998 and an admission rate of 1.2%.

3.2 Chart Selection and Review

Eligible patient visits were identified by searching Emergency Department records from the 1998 calendar year at both hospitals using search terms taken from the World Health Organization's International Classification of Diseases. It was felt that a one-year study period would accurately capture the current clinical practice and would remove any seasonal variation in prevalence or treatment and admission patterns. Charts with diagnostic codes 680 (carbuncle furuncle), 681 (cellulitis and abscess of finger and toe), 682 (other cellulitis and abscess), 683 (acute lymphadenitis) or 684 (impetigo) were identified and reviewed by two reviewers.

3.3 Inclusion and Exclusion Criteria

Reviewed charts were included for analysis if they had evidence of cellulitis, erysipelas, wound infection or cutaneous abscess diagnosed and treated in the Emergency Department. Patients were assigned a diagnosis of “abscess” if there was any mention of purulent drainage, or any record of an incision and drainage (with release of purulent material) performed in the Emergency Department. Patients were assigned a diagnosis of “wound infection” if there was any mention of recent trauma to the infected area. Patients were assigned a diagnosis of erysipelas or cellulitis if the attending Emergency Physician had used these specific terms on the Emergency Department record and there was no mention of prior trauma or incision and drainage during the visit.

Charts were excluded if the patient was less than 15 years old, did not have one of the above diagnoses or was treated directly by a specialty service and not evaluated or treated by the Emergency Physician.

3.4 Data Abstraction

Data was abstracted from the charts by either one of the two reviewers using a standardized data abstraction form and then entered into a computerized database. Unclear documentation or questionable charting was resolved by consensus between the two reviewers. If a particular characteristic or clinical sign was not recorded on the chart, it was entered into the database as being absent.

3.5 Outcome Measures

The primary outcome identified in this study was the route of antibiotic therapy chosen (intravenous versus oral). Other outcomes recorded included admissions to

hospital, consultations to specialty services, number of visits to the Emergency Department, change in diagnosis and complications.

3.6 Statistical Analysis

Descriptive statistics including proportions, means and 95% confidence intervals were calculated. Univariate predictors of intravenous therapy were identified using Chi-square statistics (or Fisher's Exact tests).

4. Methods (Prospective Study)

4.1 Design and Setting

This was a prospective cohort study, also conducted in Kingston, Ontario at its two hospital sites and Emergency Departments: Kingston General Hospital (full service inpatient care) and Hotel Dieu Hospital (outpatient day hospital). These hospital sites comprise the tertiary care teaching hospitals for the Emergency Medicine Program at Queen's University. The Emergency Departments are staffed 24 hours a day with fellowship trained Emergency Physicians and training residents. These hospitals together had more than 90,000 Emergency Department visits at both sites during the years 1999 and 2000. Patient recruitment took place between the 1st of November 1999 to the 31st of July 2000 (eight months total).

4.2 Patient Selection

Patients were approached for entry into the study at both Emergency Departments. The goal for recruitment was to obtain a consecutive sample of patients with cellulitis presenting to the Emergency Departments over a six-month period. Patients were approached during all 24 hours of operation from Monday to Friday. A

research nurse was available for assistance with data entry forms and clinical measurements from 0800 to 2200 Monday to Friday. Due to the unavailability of the research nurse and high patient volumes on weekends, patients were not entered into the study if their first visit to the Emergency Department occurred on Saturday or Sunday. The Emergency Physicians at the study centres did, however, agree to complete data forms for patients already being followed within the study who were scheduled to receive intravenous antibiotics on the weekend.

Staff training sessions were held at Emergency Department teaching rounds for three consecutive weeks in order to orient the Emergency Physicians and residents to the study and the data collection forms. Information packages were posted in the Emergency Department nursing lounge and at the registration desk to remind the nursing and reception staff about the study and alert the physicians when potential study patients registered at the Emergency Department.

4.3 Patient Eligibility

4.3.1 Inclusion Criteria

Patients eligible for inclusion were diagnosed with a skin infection by the attending Emergency Physician or senior Emergency Medicine training resident. They had documented evidence of at least three of the signs and symptoms listed below. These signs and symptoms were present for no longer than one week prior to seeking treatment.

- 1) Erythema (redness) in a well localized area
- 2) Localized induration or swelling
- 3) Pain at rest or with palpation of the affected area
- 4) Palpable heat or warmth at the infection site

- 5) Purulent drainage from a traumatic wound
- 6) Lymphangitis (red streaking following the line of the lymphatic drainage system) and/or palpable lymphadenopathy (swollen lymph node proximal to the infection site)
- 7) Fever of 38°C or greater, either reported by the patient or documented in the Emergency Department
- 8) Systemic symptoms of infection (including but not limited to nausea, vomiting, malaise and myalgias)
- 9) Abscess (a localized collection of subcutaneous pus) after an incision and drainage procedure with greater than one centimeter of surrounding erythema and or signs of lymphangitis

In summary, patients with new onset of signs and symptoms consistent with cellulitis, erysipelas, abscess with associated cellulitis (after incision and drainage) and/or non-surgical wound infections were eligible for study entry.

4.3.2 Exclusion Criteria

Patients with the following signs and symptoms were excluded from study eligibility.

- 1) Any signs and symptoms consistent with necrotizing fasciitis such as:
 - (a) severe pain (out of proportion to the observed physical signs of infection)
 - (b) marked systemic signs of infection and inflammation (high temperature, tachycardia, tachypnea, hypotension)
 - (c) evidence of septic shock and circulatory collapse
 - (d) visible necrosis of the overlying skin

Rationale: Necrotizing fasciitis is a life and limb threatening condition requiring emergent surgical intervention and aggressive antibiotic therapy (reference, see introduction). The management priorities are markedly different for this infection than for patients with less severe soft tissue infections. Patients suspected of having necrotizing fasciitis should not be part of this study.

2) Children less than 16 years old.

Rationale: Children less than 16 years old require the consent of a parent or guardian to participate in research studies. Skin and soft tissue infections do occur in children but are much less common, and occasionally are caused by different organisms than skin infections seen in adults.⁸ It was felt that very few additional patients would be recruited by adding children to the study.

3) Pregnant women or breast-feeding mothers.

Rationale: Although the antibiotics used in the study are known to be safe in pregnant and nursing mothers, and the treatment priorities unlikely to be different from other eligible patients, the Queen's University Research Ethics Board requested that this group of patients be excluded.

4) Patients with post surgical wound infections.

Rationale: Patients with post-surgical wound infections may be treated differently than patients with traumatic wound infections. Referral to a specialty service for assessment was one of the outcome measures of this study, and patients with post-operative wound infections are often referred back to the surgical service performing the procedure, even if the infection is relatively minor. This practice had the potential to bias the outcome

measure: thus patients without post-operative wound infections were not included in the study.

5) Infection at the site of a recent animal or human bite wound.

Rationale: Animal and human bite wounds become infected with different organisms than other wound infections. These infections are treated with different antibiotics, and frequently require surgical intervention.

6) Infection arising in diabetic foot ulcers or decubitus ulcers.

Rationale: Same as exclusion number 5.

7) Suspected underlying osteomyelitis or septic joint.

Rationale: Patients with osteomyelitis or septic (pus-filled) joints require surgical intervention for diagnosis and treatment, and then need prolonged intravenous antibiotic therapy (often in excess of six weeks duration) for complete resolution of the infections.

8) Non-infectious diagnosis ultimately thought to be responsible for symptoms.

Rationale: Although the issue of identifying patients without infections whose symptoms mimic those of cellulitis is an important one, patients with non-infectious diagnoses are clearly not part of the population of interest for this study.

In summary, the target population for this study was the group of patients with uncomplicated skin infections, which would be expected to respond to antibiotic therapy aimed against the two common groups of organisms responsible for this infection (*Staphylococcus aureus* and Group B Streptococcal species). This group is certainly heterogeneous in terms of infection cause, severity and host risk factors and co-morbidities. Most of the exclusion criteria were designed to keep the study population as

similar as possible. Patients with skin or soft tissue infection that would clearly have different treatment approaches and priorities were therefore excluded.

4.4 Ethical Considerations

This project received approval from the Queen's University Research Ethics Board (Appendix A). The research nurse and/or the attending Emergency Physician on duty approached eligible patients. Patients were asked for their written consent to participate in the study, as requested by the Research Ethics Board. Patient confidentiality was maintained throughout the study, and any identifying characteristics were removed from the study records. Patients who returned for repeated doses of parenteral antibiotics and/or further measurements of their infection had their parking costs covered to help improve patient compliance with follow-up, and help to offset the inconvenience to the patient of multiple visits.

4.5 Antibiotic Treatment

Patients were treated either with intravenous or oral antibiotics according to the decision of the attending Emergency Physician. If the physicians decided to treat with intravenous antibiotics, they were asked to choose either cefazolin (Ancef) 2 grams with 1 gram of probenecid or ceftriaxone (Rocephin) 1 gm. These two treatment regimens are both widely used in the Emergency Department treatment of cellulitis and allow for once daily visits and antibiotic dosing.²

Although it would have been preferable to have all patients treated identically, informal discussion amongst Kingston Emergency Physicians revealed varying opinions about the two intravenous antibiotic regimens. Despite a lack of evidence favouring either regimen there were very strong preferences among the physicians for one or the

other. It was felt that insisting on the use of only one of these two regimens would potentially alienate some of the physicians, and therefore reduce cooperation and enrollment. Since the success of this study depended on the participation of the physician group in Kingston, we permitted the use of both of the two antibiotic regimens described above in our study patients.

Physicians were given dosing guidelines for several oral drugs felt to be acceptable choices in the treatment of cellulitis, to ensure that any treatment failures were not the results of inadequate dosing. They were asked to choose cefalexin (Keflex) 500 mg orally four times per day as the first line drug. Several other choices were given, primarily to ensure that patients who reported an allergy to cefalexin would still be included in the cohort and treated appropriately.

4.6 Data Collection

4.6.1 General Description

The following information was collected from eligible patients identified in the Emergency Department: patient demographics and associated medical conditions, history of the infection and any previous attempts at treatment (including prior antibiotics and or incision and drainage). Baseline physical examination was performed, and data collection forms with specific objective measurements were completed every day that the patient was seen in the Emergency Department (appendix B).

Some of the enrolled patients with more minor infections were assessed by the Emergency Physician and treated with oral antibiotic therapy (rather than intravenous), and subsequently discharged from further Emergency Department evaluation. These patients had an initial set of measurements performed in the Emergency Department

during their visit. They were subsequently contacted three days after their Emergency Department visit and asked to return for one more set of measurements with the hope of obtaining serial measurements on patients with less severe infections.

4.6.2 Objective Measurements

These measurements were developed and chosen to be a comprehensive representation of the elements of skin infections (previously described in the introduction): warmth, redness, pain, swelling, and manifestations of local or systemic spread of the infection. They were taken and recorded by the attending physician or the senior Emergency Medicine training resident. The research nurse assisted with the use of the thermometer and other equipment, and prompted the physicians to complete the data forms and took the photographs of the infections. The goal of the study was to obtain daily measurements for the duration of the patient's Emergency Department treatment. The objective measurements included:

- 1) Area of erythema (cm^2). This was calculated by taking the product of the largest diameter of erythema, and the cross-sectional diameter perpendicular to it. This was measured with a tape measure.
- 2) Largest change in diameter of erythema, measured in cm, outside or inside a marker margin drawn at the patient's first visit.
- 3) Temperature difference, in degrees, between the infected area of body and the skin on the uninfected opposite side (mirror image), measured with a non-invasive skin probe.
- 4) Patient pain assessed using a 10 cm Visual Analogue Scale.

- 5) Visual intensity of erythema as compared to a computer-generated chart, showing a gradient of five red tones. This was developed using digital photographs of the skin infections of several Caucasian patients, and their uninfected skin. The most intense redness was used at one end of the scale (5) and normal uninfected skin tones were used at the other end (1). This scale is shown in Appendix C.
- 6) (a) Presence, absence of fever (temperature $> 38^{\circ}\text{C}$ either in ER or documented at home by patient)
(b) Presence, absence of other systemic symptoms of infection (nausea, vomiting, myalgias)
(c) Presence, absence of lymphadenopathy or lymphangitis
- 7) The patient's perception of improvement, assessed using a 5-point Likert Scale
- 8) Daily photographs of each patient's infection, taken in a standardized fashion (3 to 4 feet away, using a flash, followed by a close-up from within one foot) with a digital camera
- 9) Physician impression of the likelihood of abscess formation, assessed using a five point ordinal rating scale
- 10) Physician impressions of infection severity, on a five point ordinal rating scale
- 11) Other relevant clinical information (dose and type of antibiotic used, consultation with specialist, need for incision and drainage or other surgical procedure, admission to hospital).

4.6.3 Inter-Rater Agreement:

Inter-rater agreement assessments for these measurements were performed on a convenience sample. For these measurements, two separate physician observers

completed identical data collection forms for the same patient. Each physician was blinded to the other set of measurements. These second physician data forms were completed by a convenience sample of the attending physicians and senior Emergency Medicine training residents working at both Emergency Department sites. Study nurses attempted to obtain duplicate measurements for all patients in the study by approaching the second physician on duty. The ability of this physician to participate in duplicate data collection depended on the level of activity elsewhere in the Emergency Department (i.e. on days when the Emergency Department was busy, physicians could refuse to participate in inter-rater measurements due to time constraints).

4.7 Outcome Measures

4.7.1 Treatment Failure

As discussed in the introduction, there are no validated definitions of treatment failure in the published cellulitis literature. We devised the following pragmatic and credible definition based on expert opinion identified in our literature review, and on our own observation of treatment patterns in this centre.

Study patients were divided into two categories based on their clinical course. Patients were classified as *clinical responders* if they improved on the therapy initiated at the first visit and were discharged from Emergency Department evaluation. Patients were labeled *treatment failures* if they required any of the following: specialist consultation, hospital admission, a change in antibiotics or a surgical procedure. A change in antibiotics was defined as an ‘upgrade’ to intravenous antibiotics from oral, or a change from one intravenous antibiotic to another. Patients who required a change in antibiotics due only to an adverse effect from their antibiotic (and not a failure to

improve) were classified as clinical responders if they did not have any of the other criteria listed under treatment failure.

4.7.2 Treatment-Based Severity Classification

Patients were given a severity classification according to the most aggressive treatment they received for the duration of their illness. Again, since there are no severity classification schema currently in use, we devised our own treatment-based severity classification. Patients successfully treated with oral antibiotics alone were labeled 'mild,' patients successfully treated with intravenous antibiotics in the Emergency Department (and not referred for consultation or admission) were labeled 'moderate' and those who required specialist consultation and/or admission to hospital were labeled 'severe.'

Patients referred for home intravenous antibiotic therapy were also classified as 'severe.' The rationale for this was that the home intravenous therapy program in Kingston is designed to provide long term home based intravenous antibiotic therapy. Patients enrolled in the program receive a minimum of 5 days of intravenous antibiotics and are generally followed by infectious disease specialists. Patients referred to the program were thus assumed to have more serious infections than patients treated with Emergency Department-based intravenous therapy.

4.8 Patient Follow-up

Study personnel attempted to contact all entered patients by telephone one week after discharge to ensure that their infection had continued to resolve as expected. Patients who did not report complete resolution of their infectious symptoms or who reported a worsening in symptoms were asked to return to the Emergency Department for

a re-evaluation. The hospital medical records of all study patients not successfully contacted were reviewed at the end of the study period to check that they had not had an unexpected Emergency Department visit for re-evaluation of their infection.

4.9 Sample Size

The study enrolled eligible and consenting patients for an eight-month period between November 1999 and July 2000. A brief chart audit (personal review) showed that there were between three and six eligible patients per week at the combined Hotel Dieu and Kingston General Hospital Emergency Departments. The goal of the study was to enroll at least thirty patients treated with intravenous antibiotics who had three or more days of data. This sample size was selected on the basis of feasibility: six months was felt to be a manageable time frame within which we could complete a pilot study testing our outcome measures. We assumed an enrollment rate of 66% and estimated that six months of data collection would enable us to enroll 30 patients receiving intravenous therapy for at least three days.

Although patient recruitment was not a problem, physician compliance with filling out data forms for repeat visits was poor, despite the presence of study nurses in the Emergency Department for 70 hours per week. The study period was extended to eight months to attempt to increase the numbers of enrolled patients with complete data collection forms for each Emergency Department visit. Despite lower than projected data form completion rates the study was stopped at the end of July 2000, when ethics approval from the Queen's Research Ethics Board expired.

4.10 Data Analysis

4.10.1 Objective 1 (description of population)

Patient demographics and associated medical conditions, average duration (days) of Emergency Department evaluation and treatment, and the rates and types of complications were evaluated using descriptive statistics, including proportions, means standard deviations, as well as 95% confidence intervals.

4.10.2 Objective 2 (*physician agreement in assessing infections*)

The reliability of the selected cellulitis measurements was evaluated on the sample of patients who had second physician data forms completed. The percentage agreement for each variable was calculated. Kappa statistics were calculated for dichotomous variables and intraclass correlation coefficients (one way random effects model) for the continuous variables. The one-way random effects model was chosen as it best reflected the clinical situation in this study, where “each target is rated by a different set of k judges, randomly selected from a larger population of judges.”⁸⁸ Data collected on the severity of infection, intensity of infection and the likelihood of abscess (using five-point rating scales) were analyzed twice: initially splitting the scales into dichotomous values and calculating Kappa statistics and secondly using the ordinal scale as a continuous variable and calculating intraclass correlation coefficients.

4.10.3 Objective 3 (*Defining a normal clinical course*)

The discriminant validity of the selected measurements was evaluated by examining which measurements appeared to discriminate between patients who improved as expected (*clinical responders*) over the course of the treatment and those who did not (*treatment failures*). The definition of treatment failure is described in the methods section. Only patients who had data recorded for more than one Emergency Department visit were included in this section of the analysis. Dichotomous variables were recorded

and proportions were compared between the two groups for each visit using the chi square and Fisher's exact tests. Since there was considerable heterogeneity within this population (every patient had different lengths of Emergency Department treatment, some patients had incomplete data forms, and the time frame in which patients reached the definition of treatment failure was variable) it was not possible to analyze the continuous variables using standard techniques for analysis of variance (ANOVA) or linear regression with time as an independent variable.

The proportions of clinical symptoms and mean measurements between the two groups were compared over the first three study days using chi-square, Fisher's exact tests and Student's t-tests (using the pooled or separate variance estimate accordingly after assessing equal variances using Levene's test). Two other specific analyses were performed to capture the difference between the two groups over time.

First, slopes for the area and diameter of erythema tracked over time were calculated for each individual patient. Additionally, a ratio variable was calculated for the area and diameter of erythema. This was calculated using the measurement at first visit divided by measurement at last visit for clinical responders, and measurement at first visit divided by measurement on the day the patient was classified as a treatment failure for treatment failures. These four variables (the ratio and slope variables for the change in area and the diameter of erythema) were examined using frequency distribution tables and histograms. The assumption of normality was tested using the ratio of the skewness and kurtosis statistics with their standard error. If the hypothesis of normal distribution was confirmed, the mean ratios between the two groups were then compared using a

Student's t-test. Otherwise, the means were compared and tested using the Mann-Whitney U-test.

4.10.4 Objective 4 *(evaluating infection severity)*

The data from the first Emergency Department visit for all study patients were used to evaluate the criterion validity of each of the measurements when compared to physician treatment decision. Treatment decision was used as the gold standard to divide patients into three mutually exclusive groups: mild, moderate and severe (discussed above under the heading 'severity classification'). The individual measurements were then evaluated to see which ones best reflected this gold standard. Proportions were compared using Chi square and Fisher's Exact tests while the means of continuous variables were compared using Student's t-tests and Mann-Whitney U-tests. Receiver Operator Characteristic (ROC) curves were also constructed to identify potential cut points in severity assessment.

4.10.5 Objective 5 *(predicting treatment failure)*

The data from the first Emergency Department visit for all study patients were used to identify univariate associations between historical features, co-existent illness, clinical characteristics and the clinical outcome of treatment failure. Treatment failure was defined as in objective 3. Proportions were compared using Chi square and Fisher's Exact tests while the means of continuous variables were compared using Student's t-tests and Mann-Whitney U-tests.

5. Results (Chart Review)

5.1 Search Results

Objective 1 (description of the population and identification of treatment failure rate) was evaluated using data obtained from the chart review. Seven hundred sixty eight charts were identified using the described search terms. Three hundred twenty-three records were excluded after initial assessment, and reasons for exclusion are outlined in Table 1.

5.2 Overview of Population and Consultation / Admission Rates

The study population then consisted of 445 infections in 426 patients (19 patients had two episodes of infection during the year). After review of the 445 study charts, the initial diagnosis was assigned based on the first Emergency Department visit. The demographics and relevant historical and physical findings of the study patients are summarized in Tables 2(a) and (b). There were 51 specialty consultations in 49 infectious episodes (11%), with 2 patients receiving multiple consultations. Twenty-six consults were directed toward a surgical service (orthopedics, general surgery or plastic surgery), 10 to the infectious disease service and 25 to internal medicine. Thirty-three patients (7.4%) were admitted to hospital for treatment (no patients were admitted more than once in the study period).

Six patients (1.3%) had a final diagnosis that differed from the Emergency Department initial diagnosis. Five patients initially diagnosed with cellulitis were ultimately diagnosed with osteomyelitis (3 patients) or septic joint (2 patients). One

patient, initially diagnosed with an abdominal wall abscess, was ultimately diagnosed with an abdominal wall hernia. These six patients were all referred for consultation.

5.3 Antibiotic Routes, Location of Administration and Treatment Failure Rate

One hundred and seventy cellulitis episodes (38.2%) in 165 patients were treated with at least one dose of intravenous antibiotic therapy. In total, this treatment required 425 Emergency Department visits with a mean 3.2 visits (95% Confidence Interval 2.9-3.6) per episode of infection. The rate of treatment failure for Emergency Department-based intravenous treatment was calculated to be 47/170, or 27.6%.

5.4 Sample Size Calculation

A future clinical trial comparing Emergency Department-based intravenous antibiotic therapy with regimen of a single dose of intravenous antibiotic followed by oral therapy should be designed and performed as an equivalence trial. Jones et al commented that "in equivalence testing the relevant hypothesis is that a difference of at least Δ exists, and the trial is targeted at disproving this in favour of the alternative hypothesis that no difference exists."⁸⁹ Calculation of the sample size, then, involves selecting a value p (the percentage of expected successes if both treatments are equal), and the value of the difference, Δ , felt to be clinically important. If the treatments are in fact equal then the upper 100 (1 - α) % confidence limit for the difference in percentage successes will not exceed Δ with probability 1 - β .

Sample size can then be calculated using the formula:

$$n = \frac{2p * (100-p)}{\Delta^2} * f(\alpha, \beta)$$

Setting α at 0.05 and β at 0.1, $f(\alpha, \beta) = 10.5$

We will assume a significant difference of 10% for Δ and 72% for the value of p . This yields a sample size of 423 patients per group.

5.5 Identifying Factors Associated with Intravenous Antibiotic Therapy

In order to evaluate the factors associated with intravenous antibiotic therapy (versus oral therapy) in this patient population, infections treated without antibiotic therapy or treated only with topical antibiotics were removed from the study group. Sixty-six infections were removed for this reason, leaving 379 infections in 367 patients. Tables 3(a) and (b) outline the significant differences (on univariate analysis) between the patient characteristics and infection features of the infections treated with intravenous antibiotics versus those treated with oral antibiotics. These univariate comparisons have not been adjusted for multiple comparisons.

In summary, 768 charts were reviewed and 323 were excluded leaving a total study population of 445 infections in 426 patients with Emergency Department assessments for skin and soft tissue infections in the 1998 calendar year. One hundred and seventy infections (38.2%) were treated with at least one dose of intravenous antibiotics. Factors associated with intravenous versus oral antibiotic therapy (on univariate analysis) included: the presence of co-morbidities such as diabetes and immunocompromise, a history of fever, chills or vomiting and prior antibiotic treatment of the infection. Other associated factors included the presence of lymphadenopathy or lymphangitis, fever in the Emergency Department, an elevated white blood count ($>10 \times 10^5$) and infection located on the foot. The failure rate of Emergency Department-based intravenous therapy in this patient sample was calculated as 27.6%. Using a failure rate of 28% and a clinically significant difference of 10% between treatment regimens, setting α

at 0.05 and β at 0.1, the sample size for a future clinical trial would be 423 patients per group.

6. Results (Prospective Study)

6.1 Summary of Patient Population

6.1.1 Enrollment and Exclusions Overview

During the eight-month study period (November 1999 to July 2000 inclusive), 84 patients with 86 episodes of cellulitis agreed to be followed in the study, and had one or more data collection forms filled out. Six patients were excluded from analysis, for the following reasons:

- 2 patients were ultimately diagnosed with an alternate, non-infectious diagnosis felt to be responsible for their symptoms.
- 2 patients had infected animal bite wounds
- 1 patient had an infected diabetic foot ulcer
- 1 patient had a post-operative wound infection

These conditions had all been specified as ineligible before the initiation of the study in an attempt to obtain an homogeneous patient population. Figure 1 shows a chart summarizing patient enrollment and outcomes.

6.1.2 Treatment of Patients with Two Episodes of Cellulitis During the Study Period

Two patients each had two separate episodes of cellulitis within the study period, and were therefore entered twice. The two episodes were separated by a long period of time in both cases: the first patient had two episodes 4 months apart and the second patient's episodes were 5 1/2 months apart. Due to the time delay between infections it

was determined that both patients had suffered from two distinct infections, rather than a recurrence of the initial infection. Both patients had been successfully contacted by the study nurses after the first episode and had reported complete or near complete resolution of symptoms in the two-week period following the initial episode.

The decision was made to include all four episodes in the data analysis for two reasons. Firstly, there appears to be a significant population of patients who suffer from repeat episodes of cellulitis – indeed, one quarter of our study population reported at least one previous experience with cellulitis, and nearly all of these patients reported the infections occurring in the same physical location. These two patients therefore represent a large group of patients with recurrent cellulitis, and including both episodes from each patient potentially enhances the external validity and generalizability of the study results. Secondly, the primary focus of the study was on the evaluation of the clinical course of these episodes and not on eliciting their cause, as would be the case in an etiologic study. Although the inclusion of repeat infections has the potential to bias any conclusions one may make about the etiology of a disease through the potential duplication of important patient characteristics, we do not feel that this is an important concern when the primary focus is the course and outcome of an episode of cellulitis. Since the focus of the study was to evaluate the markers of severity and clinical decision-making process for the episodes of infection presenting to the Emergency Department during the study period it was decided to include the two repeat infections.

6.1.3 Study Population and Breakdown of Data

The resulting study population therefore consisted of 80 infections in 78 patients. It is indicated throughout the manuscript whether the focus of discussion is patient

characteristics (where the study group consists of 78 patients) or infection characteristics (where the study group consists of 80 infections).

The 78 patients in the study group made a total of 215 Emergency Department visits for assessment and treatment of their infections. One hundred and seventy six data forms were completed during these visits, for an overall completion rate of 81.9%. Nineteen duplicate (interobserver) measurements were recorded during the study period, representing 11% of all data forms. Serial data collection (data from more than one Emergency Department visit) occurred in 50 of the infectious episodes (49 patients), representing 64% of the 80 infections studied.

6.1.4 Substudy Population Breakdown

In order to address the specific objectives of the thesis, the data were divided into three separate databases (referred to as substudies). These different subsets of patients were used in researching objectives 2 to 5. Objective 2 (assessing physician agreement) was examined using the substudy of 19 patients with duplicate data forms. Objective 3 (defining the normal clinical course and evaluating objective measurements) was evaluated in a substudy of the 50 infections with serial data from repeat visits. Objectives 4 and 5 (description of patients, assessment of severity and predictors of treatment failure) were addressed using the entire study population of 80 infections.

The demographic data and co-morbidities of the 78 study patients are shown in Table 4(a). The historical features and physical exam findings associated with the 80 episodes of cellulitis are summarized in Table 4(b). The tables are broken up to illustrate these features across each of the three substudies described above.

6.2 Analysis by Objectives

6.2.1 Overview of Study Population, Treatment and Clinical Outcomes for the Prospective Study

The patient demographics and clinical features of infection for the study population of 78 patients (with 80 episodes of cellulitis) are displayed in the left-hand column of Tables 4(a) and 1(b). The majority of patients (60%) were male with a mean age of 49. The most common reported co-morbidities were peripheral edema (15%) and a pre-existing dermatologic disorder (10%). As previously mentioned, 21 patients (26%) in the study group reported a previous episode of cellulitis. Of these 21 patients, information about previous infections was documented in 17. Fourteen of the 17 patients reported a previous episode in the same anatomic location.

Nearly half of the patients (44%) reported a history of some kind of trauma to the area prior to developing cellulitis, although only 13% had an overt laceration. Interestingly, 10% of patients reported a history of blunt trauma without evidence of any disruption to the skin barrier. Seventy-six episodes (95%) of cellulitis occurred on the extremities. Of the 80 episodes of cellulitis included in the study, 53 (66%) received IV antibiotics and 10 (13%) required hospital admission. These 10 patients were admitted under the following specialty services: four patients to Internal Medicine, three under Orthopedic Surgery, two to Vascular Surgery and one to the Plastics/Hand Surgery service.

6.2.2 Patient Follow-up:

Of the 70 patients discharged from Emergency Department care, 48 (68.6%) were successfully contacted and all reported their infection to be completely resolved or

significantly improved. Those patients who were not contacted had their medical records reviewed one month after the completion of the study. None of these twenty-two patients had documentation of reassessment or further treatment of their infection in a Kingston Emergency Department. These patients were therefore assumed to have continued to improve, and were classified as clinical responders.

6.2.3 Treatment Failure Rate

Forty-six of the 80 episodes of infection were initially treated with Emergency Department-based intravenous antibiotics. Based on the classification for treatment failure described in the Methods (change in treatment, additional surgical procedure, consultation or admission to hospital), the rate of treatment failure in the prospective study population treated with Emergency Department-based intravenous antibiotics was 12/46 episodes of infection or 26.1%. Twenty-nine of the patients were initially treated with oral antibiotics; 2 ultimately required intravenous antibiotics, for a treatment failure rate of 6.8% in the oral antibiotic-treated group.

6.2.4 Summary

In summary, the study enrolled 78 patients with 80 episodes of infection over an eight-month study period. More than half (56) of these infectious episodes were treated with intravenous antibiotics and 10 patients were admitted to hospital for treatment. The rate of treatment failure for patients treated with the Emergency Department-based intravenous antibiotic regimen was 26.1%, and 6.8% in the patients treated with oral antibiotics.

6.3 Do Physicians Agree in Their Assessment of the Clinical Features and Characteristics of Cellulitis? (Objective 2)

6.3.1 Overview of Substudy Population

Second physician data forms were completed during 19 patient visits (10.6% of all completed data forms). Calculated measures of agreement for the data entered on the duplicate forms are summarized in Table 5(a) and 5(b).

There is some disparity in the percentage of agreement (overall very high) and the calculated statistics for agreement (Kappa and ICC coefficients which range from very good to extremely poor) in the variables studied. This is evaluated in more detail in the discussion, but reflects the low prevalence of the specific characteristics of interest in the interobserver substudy. The breakdown of the responses in the two physician assessments for the interobserver substudy may be seen in Table 5(a).

6.3.2 Physician Agreement: Dichotomous and Ordinal Variables

The agreement between physicians on the presence of fever, the presence of systemic symptoms and the likelihood of abscess were high, with Kappas of 1.0 and 0.73 respectively. There was moderate agreement in the five point ordinal scale of physician severity assessment. This was measured using both a Kappa (0.35) for the dichotomized scale and an ICC (0.39) using the scale as a continuous variable. There was also moderate agreement in the physician assessment of need for admission (Kappa of 0.46). The relatively large standard error suggests that a larger sample is required to confirm this trend.

6.3.3 Physician Agreement: Continuous Variables

The continuous measurements (surface temperature, diameter of erythema and VAS pain) taken of the patients' infections appeared highly reliable, with intraclass correlation coefficients of 0.90, 0.98 and 0.95. The intensity of erythema, measured on a 5 point ordinal rating scale also appeared to be very reliable with a Kappa of 1.0 and an ICC of 0.89.

6.3.4 Summary

In summary, the agreement between physicians on the characteristics of cellulitis infection is very strong when objective measurements are used (such as diameter of erythema) while the agreement appears to be moderate when physicians are asked for a subjective clinical impression (such as an impression of severity). The small sample size and resultant large standard errors for the dichotomous and categorical variables mandate further evaluation, but the trend of the results implies a need for objective measurement of the manifestations of these infections and for concrete clarification of the features of severity and admission requirements.

6.4 Can We Define the Normal Clinical Course of Cellulitis and Identify Deviations From this Course that Constitute Treatment Failure? (Objective 3)

6.4.1 Multiple Visit Substudy: Patient Population and Demographics

Fifty-four patients with 55 separate episodes of infection visited the Emergency Department more than once for treatment of their infection. Of these 55 infectious episodes, serial data recording the trend of the infection were available for 50 (i.e. data were recorded for more than one visit in 50 of 55 episodes of infection. These 50 episodes of infection (in 49 patients) comprise the "multiple visit substudy" referred to in

section 3.1.3. The demographic features in this group of 49 patients are compared with the 29 patients not included in the multiple visit substudy in Table 6(a). The demographics of this population are not significantly different from the overall study population.

6.4.2 Comparison of Multiple Visit Substudy with Overall Study Population

The specific clinical features of these infections are compared between the entire population and the multiple visit substudy in Table 6(b). The multiple visit substudy contains the majority of patients treated with intravenous antibiotics (45 of possible 53 episodes of infection requiring intravenous antibiotics). It is expected that patients with these infections would appear sicker than their oral antibiotic-treated cohort. Consequently the patients in the multiple visits substudy have a higher percentage of fever and systemic symptoms than those patients not included. The mean area of redness is also larger in these patients (688cm^2) than in those patients not included (335cm^2).

6.4.3 Treatment Failure Rate and Type of Intervention

The 50 episodes of infection in this substudy were divided into two groups: “treatment failures” or “clinical responders” as described in the methods, section 7.1. Thirty-seven infections met the criteria for “clinical responder” while 13 were classified as “treatment failures” for a treatment failure rate of 26% in this substudy.

The number of days of Emergency Department treatment in both groups completed in each group is shown in Table 7, and the type and treatment day of the second intervention in the treatment failure patients is shown in Table 8. It must be noted that 12 of the 13 treatment failure patients had undergone a change in treatment or second intervention by the third day of Emergency Department treatment. This implies

that there was some measurable change or lack of change in the clinical course prompting the Emergency Physicians to intervene in these patients. The analysis in this section focuses on identifying any characteristics that separate these patients from the cohort of patients who continued on their initial treatment path without changes or subsequent intervention.

6.4.4 Clinical Symptoms – Comparison Between Treatment Failures and Clinical Responders

Table 9 shows the comparison of clinical symptoms in the two patient groups. None of the clinical symptoms were found to be significantly different between the two groups, over any of the first three days of treatment.

6.4.5 Physical Signs: Comparison Between Clinical Responders and Treatment Failures

Table 10 shows the comparison of the measured infection characteristics between the Clinical Responders and the Treatment Failures over the first three days of treatment. The only continuous measurements that showed a statistically significant difference between the two groups are the measurements of the size of erythema (specifically the largest diameter and the area). Boxplots displaying the data for these two measurements were constructed. Figures 2(a) and 2(b) show the area of erythema for the Clinical Responder group (2a) and the Treatment Failure group (2b). Figures 3(a) and 3(b) show the largest diameter of erythema in these two groups.

There is a trend toward a significant difference between clinical responders and treatment failures in the temperature difference between infected and uninfected skin. Boxplots displaying these data are shown in Figures 4(a) and 4(b).

6.4.6 Change in Size of Infection Over Time: Clinical Responders Versus Treatment Failures

Table 11(a) shows the mean slope and area variables for the change in area and diameter over time. The comparison between the mean values was highly significant for all four different representations of the change in infection size. This result demonstrates an association between the expansion of erythema over time (as evidenced by a positive slope or ratio of 1 or greater) and the physician decision to change the therapeutic plan. Table 11(b) shows the skewness and kurtosis statistics for these four variables, and the results of hypothesis testing for the normal distribution. Receiver Operating Characteristic curves were constructed for the 4 slope and ratio variables representing change in size over time (Figures 5-8).

6.4.7 Physician Assessment of Severity

The physicians were asked to rate the perceived severity of the patient's infection each time the patient came to the Emergency Department for assessment, using a 5 point ordinal rating scale from 1 (very severe) to 5 (very mild). Boxplots showing the distribution of these results are shown in Figures 9(a) and (b), with analysis of the data displayed in Table 12.

The numbers at the bottom of each graph column represent the numbers of patients who completed the data forms on the first, second and third study day, respectively. As the study continued, the number of complete data forms drops off significantly; from 33 patients on the first day in the Clinical Responders group to 21 patients on the third day, and from 7 patients on the first day in the Treatment Failure group to 2 patients on the third day. Despite the uniformity of the responses (the vast

majority of infections are rated “moderate” by the assessing physicians), the clinical impression of severity does become significantly different between the two groups at day 3. The physicians began, on the third treatment day, to rate the infection in the Clinical Responder group as milder than the Treatment Failure group.

6.4.8 Patient Impression of Improvement

Boxplots displaying the results of patient agreement with the statement “my infection is better than yesterday” are shown in Figures 10(a) and (b), with analysis of these data also displayed in Table 12. The clinical responders who were continuing to receive antibiotics on day 3 were statistically more likely to agree with the statement of improvement, in contrast to the treatment failure patients.

6.4.9 Summary

A summary of the performance of each of the measurements under the headings “criterion validity,” “reliability” and “feasibility” is displayed in Tables 13(a) and (b). Overall, the measurements of absolute size and change in size over time were the only measurements that performed well in all three categories. The measurements of temperature difference and intensity of erythema were unable to differentiate between clinical responders and treatment failures. The subjective measurements of physician and patient impression of infection severity were much less reliable and less able to differentiate between the two groups. The manifestations of systemic or local spread (fever, systemic symptoms and lymphadenopathy or lymphangitis) also lacked criterion validity and were only moderately reliable, but this may be due to a small sample size in this patient group.

6.5 What are the Clinical Characteristics that Determine the Severity of an Episode of Cellulitis? (Objective 4)

6.5.1 Overview of the Severity Assessment and Classification Process

There were data available for the first Emergency Department visit of all 80 episodes of infection during the study period. All 80 episodes were given a severity classification according to the antibiotic route selected and the location of treatment (home, Emergency Department or hospital). This classification is described in the Methods section under the heading 'severity classification.' Patients were divided into groups based on the treatment decision made on the first Emergency Department visit (*initial severity classification*) and then again based on their ultimate antibiotic treatment requirements (*final severity classification*). For example, a patient initially placed on oral antibiotics and discharged home, but who returned to the Emergency Department and was subsequently given intravenous antibiotics and admitted to hospital would have an initial severity classification of 'mild' and a final severity classification of 'severe.'

Eleven patient infections required an 'upgrade' in their antibiotic treatment, with a subsequent change in classification. Thus 69 of the infections (86%) improved with the route and location of antibiotic administration prescribed by the Emergency Physician during the first visit. It should be noted that two episodes of cellulitis were initially treated with intravenous antibiotics, and were subsequently changed to a second intravenous antibiotic. These two patient infections were labeled as Treatment Failures in Objective 3 (Section 4), but are identified in this section as patients who were correctly classified with respect to severity, since they did not require an "upgrade" in antibiotic route or location of administration. A third patient presented with an episode of cellulitis

which improved on a regimen of Emergency Department-based intravenous antibiotic treatment. This patient was switched to oral antibiotics and suffered a relapse within two days, necessitating another short course of Emergency Department-based intravenous antibiotics. This patient's infection was classified as a Treatment Failure in Objective 3 (Section 4), but is identified in this section as an infection which was correctly classified with respect to severity, since again, it did not require an "upgrade" in antibiotic route or location of administration.

6.5.2 Comparing Infections Treated with Intravenous Antibiotics versus Oral Antibiotics

What clinical features are associated with a 'correct' treatment decision (i.e. the selection of a treatment on which the patient improves without further intervention) of intravenous antibiotics? Using the 69 infections that did not require a change in treatment, the characteristics of infections treated with oral antibiotics were compared with those who received Emergency Department-based intravenous antibiotics. (Since there were only 5 patients admitted or referred at the first visit, the numbers were too small to provide a meaningful three-way comparison). The comparison between the 27 correctly classified 'mild' infections (oral antibiotics) and the 37 correctly classified 'moderate' ones (intravenous antibiotics) is shown in Table 14.

Patients with a history of a previous episode of cellulitis were more likely to be treated with intravenous antibiotics, as were patients with a fever and/or systemic symptoms of infection and prior antibiotic treatment of this infection. There was no difference between the two groups in terms of infection location, co-morbidities such as diabetes and peripheral vascular disease, and the presence of abscess. The size of the

infection was significantly different between the two groups ($p < 0.001$), with the moderately severe group having much larger infections (mean diameter 27.3cm, 95% CI 22.7-31.8) than the mild group (mean diameter 16.3cm, 95% CI 12.2-20.3). No other measured characteristics were significantly different between the two groups of infections.

6.5.3 Evaluating the Size of Infection as a Predictor of Intravenous Antibiotic Therapy

Receiver Operating Characteristic Curves were constructed to evaluate the ability of the size of infection (as manifested by the area of infection and the largest diameter of infection at the first visit) to predict the use of intravenous antibiotics. These curves are shown in Figures 11 and 12.

Patients with any of other of the characteristics found to be significantly different between the oral and the intravenous antibiotic group were removed from the analysis. These characteristics included a history of a previous episode of cellulitis, prior antibiotic treatment of the infection and the presence of a fever and/or systemic symptoms of infection. Receiver operating characteristic curves were again constructed without these cases to test the hypothesis that the size of the infection, in the absence of any other predictor variables, was a predictor of the decision of route and location of antibiotic administration. These curves are shown in Figures 13 and 14. There was no improvement in the area under these curves. This suggests that even in the absence of the other characteristics, the size of the infection alone does not discriminate well between patients treated with intravenous and oral antibiotics.

6.5.4 Summary

Patients with a history of prior significant cellulitis, fever, systemic symptoms or previous antibiotic treatment of their infection were more likely to be placed on intravenous antibiotics than those without these characteristics. However, none of these characteristics, alone or in combination were 100% sensitive. The size of infection of patients treated with intravenous antibiotics was significantly larger than those treated with oral antibiotics, but there was no single size cut-off with good sensitivity and specificity. Even with the removal of other associated characteristics, the size of the infection alone was not a good predictor of physician treatment decision.

6.6 Are There Any Features of Infection at the First Visit That Predict Treatment Failure? (Objective 5)

Table 15(a) shows the patient characteristics of those episodes of infection (i.e. host factors) that failed treatment compared with those that responded successfully to treatment. Results that were statistically significantly different included the patient age and the presence of peripheral vascular disease. Table 15(b) shows the characteristics of the infections that failed treatment (i.e. infection factors) compared with those that responded successfully. Statistically significant results included prior antibiotic treatment, the presence of olecranon bursitis and the perceived need for initial treatment with intravenous antibiotics. The initial size of the infection was noticeably different between the groups and there was a trend towards statistical significance.

7. Discussion

7.1 Population Description and Sample Size (Objective 1)

7.1.1 Population Description:

The most striking result from the retrospective and prospective examination of Emergency Department patients with cellulitis is the heterogeneity of the patients. We attempted to create a uniform patient population by excluding patients with complicated infections (infected ulcers, bite wounds, digit infections and post-operative infection were all considered ineligible). However, even with this restricted entry criteria the variation in the patient histories and co-morbidities and infection characteristics remained impressive. Many of these common and relevant co-morbidities and infection characteristics (diabetes and peripheral vascular disease, soft tissue abscess) have been discussed in the introduction. However, the problems of how to approach patients with recurrent episodes and the impact on future trials needs to be evaluated further.

7.1.2 Recurrent Cellulitis

There were, in both the chart review and the prospective study, a large number of patients with recurrent cellulitis. This population of patients represents an obvious subgroup that should be examined further. Our chart review identified 19 patients (4.5%) with multiple episodes of cellulitis over the course of the study year, while 2 of the 78 patients in the prospective study had two episodes over the 8-month study period. Additionally, more than one quarter of the 78 prospective study patients reported having experienced a prior episode of cellulitis, nearly all in the same anatomic location.

7.1.3 Data from Other Studies

Three other studies have reviewed the characteristics of patients admitted for treatment of cellulitis. A case survey of 118 Australian patients admitted in 1991 and 1992 showed that 25.4% of the patients had a history of a prior episode.⁶⁷ A similar review in 1997 looked at 97 patients admitted with leg cellulitis and identified 9.8% patients with previous leg cellulitis.⁷¹ A third study offered antibiotic prophylaxis to 115 patients admitted to hospital with cellulitis over a 4½ year period. The recurrence rate in the 84 patients who refused prophylaxis was 19.0% versus 12.9% in patients who received monthly injections of Benzathine Penicillin G (this difference was not statistically significant). Interestingly, there was no difference in recurrence rates between those patients with an identifiable precipitating cause and those without.⁶¹

7.1.4 The Potential Effects of Recurrent Cellulitis on Outcomes in Observational Studies

These studies support our own observations that recurrent cellulitis is an important and common subgroup. These data (and our own) suggest that somewhere between 10% and 25% of patient with cellulitis can expect to have a recurrence of their disease. Are physicians more likely to choose intravenous antibiotic therapy for cellulitis infections for patients who have previously received it? It seems plausible that a combination of increased physician caution and higher patient expectations could influence choices about admission and intravenous antibiotics. This would result in a positive correlation between patients with a history of previous significant infection and an aggressive choice of therapy (i.e. intravenous antibiotics and/or hospital admission), in the absence of any other identifiable predictors.

It is also possible that a history of a prior significant cellulitis would result in increased vigilance on the part of the patient. For example, a patient with such a history may seek medical attention and antibiotic therapy for even the slightest of infectious skin symptoms, thus aborting another potentially significant episode. This awareness could potentially reverse the association of prior significant cellulitis and future significant cellulitis. This reversal in association has been referred to as “feedback bias.”⁹⁰ The significant potential for bias in the treatment decisions for patients with recurrent cellulitis should not be a problem in a randomized, double-blind clinical trial of cellulitis therapy.

7.1.5 Recommendations for Future Clinical Trials

In summary, outcomes for patients with repeated episodes of cellulitis are necessarily correlated. Studies of skin infections should identify this important historical feature, and it should be taken into account in statistical analyses. In our study, the univariate analyses addressed this issue through the separation of ‘host factors’ (demographic and co-morbidities) and ‘infection factors’ (specific features of the infectious episodes such as prior trauma, fever etc.). Thus the denominator in the analysis of host factors was the number of patients experiencing one or more events during the study period, whereas the denominator for the analysis of infection factors was the number of events during the study period.

However, this still does not completely address the issue that repeated observations for separate events in the same patients are potentially not independent of each other. Many different models using multivariate analyses can take this issue into account by adapting them to correlated dichotomous outcomes.⁹⁰ It is our conclusion that

a future clinical trial of cellulitis therapy should not exclude patients with recurrent events within the trial period. These patients, and other patients with a history of clinically significant cellulitis must be carefully identified at the time of study entry, so that appropriate consideration of these effects and statistical adjustments may be made.

7.1.6 Sample Size Calculation

The sample size calculation in the results section used the data collected in the one year retrospective review to estimate the rate of treatment failure for patients treated with Emergency Department-based intravenous antibiotics. This rate was calculated as 27.6%, and the sample size was calculated accordingly at 423 patients per study group. The rate of treatment failure in the prospective study patients treated with Emergency Department-based intravenous antibiotics was a similar 26.1%. An abstract comparing a protocol of Emergency Department-based intravenous antibiotics with a protocol of single dose intravenous antibiotic followed by oral therapy found a similar intravenous treatment failure rate of 32.4% (versus 18.9% in the oral arm).¹⁹ The only other study to look at rates of success was a second Canadian abstract, which found a smaller treatment failure rate of 12% in 346 patients treated with Emergency Department-based intravenous antibiotic therapy over a one-year period.⁵

Using a much smaller estimated rate of treatment failure (12%) but keeping the clinically relevant difference between study arms as 10%, the sample size drops to 221 patients. Since the true rate of treatment failure in our centre appears to sit between 25 and 30%, the estimate of 423 patients per study group appears to be an appropriate and conservative sample size.

7.2 Reliability Assessment for the Objective Measurements (Objective 2)

The second objective of this thesis was to evaluate the level of agreement among Emergency Physicians in their assessment of the clinical features and characteristics of cellulitis. Any measurement with poor inter-physician agreement should not be used in clinical trials, and should not be used in day to day clinical evaluation of patients with cellulitis or other skin infections. The characteristics under scrutiny would not be expected to vary over the course of one Emergency Department visit, so there should be little if any within-patient variability. The difference between the paired observations reflects the level of agreement between the two physicians, or the interrater reliability.

7.2.1 Testing the Reliability of the Dichotomous Variables

The calculated agreement between the physicians on the presence of local lymphadenopathy or lymphangitis is very poor, with a Kappa of 0. This extremely poor Kappa is initially surprising, especially given the fact that the two physicians agreed in their assessments 83% of the time. This seemingly anomalous result can be explained by the very low prevalence of this physical sign in the 19 patients sampled; this sign is reported only three times, and there are no patients in the -- cell of the 2x2 table. In other words, in each one of the three instances where one of the two physician raters reported this symptom to be present, the physicians disagreed. Since the vast majority of patients in the sample did not have lymphangitis or lymphadenopathy, the lack of any patients in the positive cells of the 2x2 table affected the calculated expected agreement in the Kappa calculation and resulted in a very low Kappa.

This effect is also seen in the calculation of a Kappa statistic for the physician assessment of severity, dichotomized into 'mild or moderate' versus 'severe.' Since there

are no patients labeled 'severe' by both physicians, the absence of any patients in the — cell of the 2x2 tables results in a Kappa of 0, despite calculated agreement between the physicians of 71% in this sample.

Another potentially misleading result occurs when we examine the apparently excellent agreement (Kappa of 1.0) between the physicians evaluating the presence of abscess. The physicians agreed every time on the presence of abscess in the 17 patients evaluated, which appears to confirm the high inter-rater reliability of this assessment. However, although the Kappa is excellent the low prevalence of abscess (only one patient) in the sample is problematic.

7.2.2 The Limitations of the Population Sample:

The low recruitment of second physicians to complete interobserver forms was a serious limitation, resulting in a small and highly selected population for the interobserver study, which was not representative of the overall study population. One cannot have confidence in an agreement statistic calculated on a segment of the population that is fundamentally different from the rest of the population, particularly when the agreement is being tested on characteristics that aren't present in the population being examined. Further study of the interrater reliability on all of these characteristics is required before we can use these measurements with any reassurance that they indeed yield consistent, repeatable measurements.

7.2.3 Testing the Reliability of the Continuous Measurements

The pairs of measurements that provided continuous data (surface temperature of infection, size of redness and patient pain on a Visual Analogue Scale) were evaluated for agreement using the intraclass correlation coefficient (one way random effects model).

These results showed excellent correlation between the two sets of measurements (all correlations were > 0.90). These excellent correlations provide some reassurance that, in addition to having a strong linear relationship, there are no identifiable systematic errors in the measurement process. The intraclass correlation coefficient, unlike the Pearson product-moment correlation coefficient, does take into account the presence of any systematic differences in measurement (or bias), and reduces the correlation coefficient accordingly.

7.2.4 Limitations of the One-way Random Effects Model

The one-way random effects model, however, cannot distinguish between the effects from the raters themselves, between the individual raters and the subjects, and those resulting from random error. Further confidence in the intraclass correlation statistic (and the reliability of the measurements) could be achieved by designing a study where a larger sample of raters each evaluates every subject. This would allow some distinction to be made between the different sources of variability, and allow a stronger estimate of the level of agreement for the continuous variables.

7.2.5 Other Limitations of the Analysis

There are two main limitations of the analysis of agreement using the intraclass correlation coefficient. The first is the tendency of the coefficient to be affected by inter-subject variability. This does not seem to have been a major factor in this sample, as the coefficients are very high despite a relatively small sample size.

The second limitation lies in the interpretation of the result – although these results are highly correlated, they are not necessarily in complete agreement. For example, the diameter of erythema measurement has a correlation of 0.97 (extremely

high), but on closer examination just 87% of the pairs of raters were within 2 centimeters of each other. The large mean diameter of redness in this sample (20.9cm) minimizes the impact of a large (and probably clinically significant) difference. The mean difference in the measurement pairs (and standard deviation) was 1.0cm (2.6cm). If we calculate two standard deviations around the mean difference, we find that the range of values that encompasses 95% of the differences is 5.2 cm. This is a very large margin of error, hidden behind an excellent correlation statistic.

7.2.6 Practical Problems Experienced with the Measurements

Why is there such a difference between the physicians when all that was required was to measure an infection with a measuring tape? Several unanticipated problems were discovered during the prospective study. Although many of the infections had very clear margins (39.5% of the pairs of measurements were identical), some had faint and poorly demarcated borders. A faint margin of infection made the decision of where to measure more challenging, and was one of the likely sources of variation between the physicians. Additional measuring problems occurred when the infection encompassed a joint since the measurements changed with the joint flexed rather than extended. It was also more difficult to choose the direction of the largest diameter when the infection was wrapped around an extremity or had an asymmetric shape.

7.2.7 Summary of Discussion Reliability Testing

Overall, the interrater analysis shows that results were more robust with continuous measures than the dichotomous ones (although this is partly explained by the reduced sample size required to reach statistical significance). The sample size was too small and selected to reach any conclusions about the reliability of any of the

dichotomous variables. Correlation of the continuous measurements, however, does not necessarily reflect agreement. Despite the excellent correlation, there were still some clinically important discrepancies in these pairs of measurements which must be highlighted –particularly the measurements of the diameter of redness, which was off by more than 2 cm in over 10% of the samples. This may be explained by some of the practical limitations of measuring skin infections.

Further research on the interrater reliability of the size of infection should utilize a larger, more representative sample – ideally with a larger number of raters who each evaluate every patient. Prospective identification of the practical problems discovered during this pilot study (i.e. poorly demarcated borders, infection encompassing a joint) during future studies would help to define their impact on the accuracy of the measurements. This would allow a more comprehensive analysis and identification of the major sources of variability.

7.3 Validity Assessment for an Evaluative Instrument (Objective 3)

The third objective of this thesis was to define the normal clinical course of cellulitis, and to identify deviations from this course that constitute treatment failure, using objective and reproducible measurements. This section of the discussion will examine the performance of the objective measurements as evaluative tools.

7.3.1 Reviewing the Gold Standard Used to Define the Clinical Outcomes

In our analysis of these variables, we used a ‘gold’ standard of physician treatment decision to define our mutually exclusive clinical outcomes of clinical response or treatment failure. To review the definition used, patients who experienced a change in antibiotic therapy, underwent a surgical procedure after the first Emergency Department

treatment day or were admitted to the home intravenous program or to hospital were all considered to have “failed treatment.”

7.3.2 Testing the First Model (Manifestations of Infection)

There were only two variables that appeared to discriminate between the two groups defined above, the single largest diameter of redness and the area of redness. On the first treatment day, both groups had mean infection sizes that were not statistically different. By the second treatment day the mean size of infections in the treatment failure group was significantly larger than the clinical responder group. This difference persisted into the subsequent treatment days, despite a rapid fall-off in the numbers of repeated measurements (a rapidly shrinking sample). The only other variable that was different between the two clinical groups was the temperature difference between infected and uninfected skin. The mean skin temperature was more than a degree higher in the treatment failure group than in the clinical responder group on the second and third day of treatment, although this value did not reach statistical significance. The intensity of redness and degree of pain measurements failed to distinguish between the two patient groups.

7.3.3 Justification for Examining Both the Diameter and Area of Infection as Size of Infection Measurements

These two measurements of size are not independent (the area of redness is clearly a function of the largest diameter), but they represent different manifestations of infection size. Although intuitively the area of erythema seems like a better reflection of the clinical situation than the single largest diameter (particularly in an asymmetrical infection), that hypothesis is challenged by the fact that any errors in the measurements of

the diameter are magnified in the calculation of the area. Additionally, the process of calculation renders the area measurement less user-friendly and prone to human error. Consequently, both measurements were studied to see if one outperformed the other in a correlation with the clinical outcome of treatment failure. Both measurements appeared to perform equally well in terms of the discrimination between the clinical responder and treatment failure groups.

7.3.4 Examining 'Change in Size' Statistics

In order to further examine the hypothesis that the size of infections that are improving will shrink, while those that are not improving will remain the same or get larger, we also compared two statistics that reflect the change in size over time. First, the slope of the change in infection size was calculated, using all measurements in the clinical responder group, and only those measurements that preceded a diagnosis of treatment failure in the treatment failure group. Secondly, a ratio variable was calculated, using the first measurement over the last measurement for clinical responders, and the first measurement over the measurement taken on the day of the 'treatment failure' intervention for treatment failures.

Both representations of the change in infection size over time were significantly different between the groups. These variables both support the hypothesis that the mean infection size in the clinical responder group decreased while the mean size in the treatment failure group increased. Receiver operating characteristic curves (Graphs 4-7) calculated for these variables have a reasonable area under the curve (all are greater than 0.80) which again supports the hypothesis that the change in size can explain a large proportion of the clinical outcome of treatment failure or clinical response.

7.3.5 Heterogeneity in the Study Population

There were two main sources of clinical heterogeneity in the patient group – first in the initial size of infection, and second in the response to treatment as demonstrated by the change in size over time. There was a huge range in the initial size of infections for both groups with very large standard deviations: 466 cm² for the area of infection in the clinical responders, and 1092 cm² in the treatment failures. There was also considerable heterogeneity in the magnitude and direction of the change in size over time. In fact, looking more carefully at the change in size over time in the two groups, we find that 32% of the clinical responders actually had an enlargement in the size of their infection on the second treatment day. Another 38% had no change over the first two days, while a decrease in size in the first two days was documented in only 30%, despite the fact that the mean change in size reflects an overall decrease.

A partial explanation for this finding lies in the way the statistics were calculated for the clinical responder patients. The data used to calculate the slope and ratio variables in this group were collected over the duration of Emergency Department treatment, and consequently would not reflect a transient worsening of symptoms if the trend over several days was one of overall improvement. In fact, if we look only at the change in size over the first two days, the difference in the slope and ratio variables is not statistically significant between the two groups. The fact that these variables did achieve statistical significance in the face of noteworthy heterogeneity (the ‘noise’), however, supports the hypothesis that the change in size (the ‘signal’) is strongly related to physician treatment decisions.

7.3.6 Problems with the 'Change in Size' Theory and Measurements

The finding that nearly one third of patients in the clinical responder group had a transient increase in the size of their infections suggests that there may be a population of patients who experience a temporary clinical deterioration before they begin to demonstrate improvement. Rather than representing treatment failure, as in our model, this may represent a version of a 'normal' course. Another third of patients had no identifiable change over the first two days, which suggests that there may be a time lag before a measurable improvement is detected in a second population of patients. If this is in fact the case, some of the patients in the treatment failure group may have been misclassified by physicians with less experience or a more aggressive approach to the treatment of skin infections. These patients who experienced a lag in signs of improvement or a clinical deterioration may have had their antibiotics changed or been referred for consultation when in fact another day or two of the antibiotic therapy they were receiving would have resulted in a visible improvement.

7.3.7 Limitations of Physician Decision as a Gold Standard

Of course, using physician decision as a gold standard has some limitations. This is a crude measurement of treatment success or failure, and highly susceptible to external influences which are separate from the patient condition (for example, physician experience and beliefs and patient expectations). The use of this 'bronze standard,' however, was justifiable in that a clinical decision in this setting was the only available indicator of patient response to treatment.

We would propose that this new concept of delay in improvement or brief deterioration prior to visible improvement should be applied to future assessments of

patients with cellulitis. In the absence of any other clinical signs of deterioration, we recommend that a patient who has an enlarging infection should be continued on the same prescribed treatment for an additional 24 hours. If this is truly a manifestation of a heterogeneous response to therapy, we should then begin to see the expected improvement, and can refine our expectations and actions accordingly. If after this interval the enlargement continues, we can then call this patient a treatment failure and act accordingly.

7.3.8 Problems with Patient Pain and Skin Temperature: the Theory and the Measurements

One other potential problem with our construct was the apparent lack of change in patient pain over time. We would expect that as the infections improved, the pain caused by the infection would lessen. However, there was no statistical significance, or even a trend, between the measured reports of pain in the clinical responder versus the treatment failure group. The most plausible explanation for the apparent failure of this measurement again lies in the issue of patient heterogeneity – there was a huge variation in the amount of pain experienced by patients with skin infections in our study. A notable proportion had minimal or no pain at the onset of treatment, while some complained of excruciating pain and were unable to walk or move the affected body part.

Patients with abscesses seemed to experience much greater amounts of pain, even after incision and drainage of the pus, than those with simple cellulitis. Elderly patients seemed to report less pain than younger patients, given a similar size of infection. The heterogeneity in our small population may have obscured the ability of the Visual

Analogue Scale pain measure to detect a difference between clinical responders and treatment failures.

A larger sample size with daily measurements over several days in all the patients would provide enough data for a multivariate analysis controlling for some of these observations. Additionally, a future study using a more refined definition of treatment failure (as discussed above) would improve the classification of patients, and may unmask the usefulness of patient pain as an evaluative tool. The same issues apply to the usefulness of temperature difference between infected and unaffected skin – a larger sample with more consistent measurements combined with a better definition of treatment failure may show the expected decrease in temperature in the infected skin.

7.3.9 Problems with Intensity of Erythema Theory and Measurements

One of the measurements evaluated in the study patients was the change in degree of redness in skin infections over time. We anticipated that as a skin infection begins to heal, the intensity of redness would diminish. This measurement failed to discriminate between patients who were improving and those who were not. This can be explained by a number of observations made during the study period.

Firstly, patients with more than trivial infections retain some degree of redness at the site of their infection for many days – no patients in the study exhibited a complete resolution of their signs and symptoms during the Emergency Department treatment phase. Therefore, a scale ranging from ‘not red’ to ‘extremely red’ would not record any results at the ‘not red’ end of the scale, even in repeated measurements over time in the same patient. We observed exactly this phenomenon, with the vast majority of readings either 3 (moderately red) or 4 (very red) for the duration of the study. This scale lacked

any sensitivity to change, or at least to any early change during the Emergency Department phase of treatment. Creating a larger scale (a nine or ten point ordinal scale) with more subtle changes in the intensity of redness might improve this measurement's sensitivity to change.

Secondly, there were a number of practical problems with the administration of this scale. Although we recognized that this redness scale would only be useful in Caucasian patients (which markedly limits the generalizability), we were unprepared for the wide variation in skin pigmentation both between and within individual patients. Even within the Caucasian population the variation in natural skin tone is impressive, and many pre-existing conditions cause changes in local skin pigmentation, particularly in the lower limbs (for example, pigmentation from arterial and venous disease in the legs may be either quite marked or diminished). Within any individual infection site there were frequently many different shades of red, and many physicians requested guidance from the study nurses in selecting the appropriate part of the infection to measure. This problem was compounded in patients whose infections were improving, since the redness at the edge of the infection would often decrease markedly, with the redness at the center remaining much more intense.

We suggest that this particular intensity of redness scale was not a useful marker of infection progress over time. The gradations of red chosen for the scale were too coarse to reflect any change that might have been present (with the majority of patient measurements clustered in the center for the duration of their study involvement). The lack of generalizability to non-Caucasian populations, the large variation in baseline skin

tones of individual patients and the large number of shades of red visible within any one infection make the scale practically difficult to use.

7.4 Testing the Second Model (Manifestations of Local or Systemic Spread)

It was hypothesized that patients failing to respond to antibiotic therapy would develop or experience persistence of the signs and symptoms representing local or systemic spread (namely fever, nausea, vomiting, chill, myalgias, local lymphadenopathy and lymphangitis). An extension of the same reasoning suggests that the persistence or new development of these symptoms would prompt a change in treatment by the treating physician. Therefore, we expected to find a higher proportion of these symptoms within the treatment failure group as the number of treatment days progressed. Surprisingly, no differences in any of these symptoms or signs were observed between the two groups.

7.4.1 Problems with Data Collection

There are some problems with the data which may have influenced the results and masked an identifiable difference between the groups. There was a rapid drop-off in available data after the second day of treatment (the number of completed forms drops from 50 on day one to 40 on day two, to 28 on day three and then to 10 on day four). This appears to have occurred for three reasons. Some patients were admitted to hospital and thus no longer followed by the Emergency Department based study nurses and physicians; some rapidly improving patients were discharged from Emergency Department evaluation after two or three days of treatment; and there were some problems with physician compliance in completing the data forms.

Since we are examining signs and symptoms that are present only within a subset of the study population, the rapid falloff in available patient measurements affected these measurements more than the ones discussed in the previous section. Additionally, the presence or absence of these signs and symptoms were recorded as dichotomous data. A larger sample size is generally required to demonstrate statistically significant differences for dichotomous data versus continuous data.

7.4.2 Credibility (or Face Validity) of this Model

The new development of signs of local or systemic spread after the first treatment day remains a highly credible component of any definition of treatment failure, regardless of our study results. Since the most feared complication of any infectious disease is the spread of the infection to the blood stream, it seems unlikely that any physician or patient would disagree with a change in treatment strategy when bloodstream spread is suspected. Less clear, however, is the duration of time to the resolution of these symptoms, once appropriate treatment has begun. Put another way, when any or all of these symptoms persist without other evidence of clinical deterioration, when do we classify the patient as a treatment failure and change the therapy?

In summary, despite the failure of our study to demonstrate a difference in the signs and symptoms of infection spread between the two clinical groups, the new development or persistence of these signs or symptoms remains a highly credible component of a treatment failure in the study of skin infections. Further study should focus on the duration of these symptoms in patients who are showing other concrete

signs of improvement. New development of any of these signs or symptoms after the initiation of treatment should continue to be part of any definition of treatment failure.

7.4.3 Summary of Discussion for Objective 3

The measurements developed to represent the clinical manifestations of infection were tested against the clinical decisions of the physicians to see if the hypothesized improvement in measurements for clinical responders and worsening in treatment failures occurred. The measurements that consistently and accurately discriminated between the clinical responders and the treatment failures were the absolute size of the infection and the change in size over time.

An unexpected finding within the clinical responder group was that approximately one third of patients experienced an enlargement of their infection, and one third showed no change over the first two days of treatment. This may represent an error in the theory that patients who are improving will immediately show improvement. Future study should test the suggestion that some patients who are responding 'normally' to treatment will experience a transient enlargement of their infection, or a lag in the visible response, for the first few treatment days. We would propose that patients in this category be observed without change in their management for a further 24 hours, provided they have no other evidence of clinical deterioration.

Several other measurements failed to distinguish between the clinical responder and treatment failure groups. These included the temperature difference between infected and infected skin and the patient's report of pain from the infection. Significant population heterogeneity may have masked the usefulness of these instruments. Further study is needed before their value as evaluative instruments is dismissed. The 'intensity

of redness' scale was not found to be useful, and in contrast to the above measurements, practical problems in the administration and the poor potential generalizability of the scale limit any future use.

7.5 Validity Assessment for a Diagnostic Instrument (Objective 4)

7.5.1 The 'Construct' of Severity

There are currently no diagnostic tests that confirm either the presence of skin infections or the severity of the infection. Patients are diagnosed by the clinicians when they exhibit some or all of the classic signs of skin infections: redness, pain, warmth and swelling.^{62-65,87}

McDowell et al have suggested that the process of validation for a diagnostic tool focus on the assessment of content validity, discriminant validity and agreement with clinical ratings.⁸¹ Since all available information about both the patients and the infections were carefully and prospectively recorded, we believe that the criterion of content validity has been satisfied. Discriminant validity, or the correct identification of differences between groups can really only be tested in the setting of a preexisting gold standard. This is again the domain of construct validity, where pre-existing hypotheses are tested against clinical outcomes, and refined accordingly.

We have initiated this process through the identification of potentially useful clinical indicators of severity. This was done by detecting associations between coexistent illness, historical features of the infection and physical findings of the infections (including all of the components of the two conceptual frameworks of infection) and the physician's correct treatment decision. It must be stressed that the associations we are identifying are between the clinical indicators of interest and a

'correct' physician decision to initiate intravenous antibiotic therapy: in other words, we are attempting to more carefully define existing clinical practice and create a more objective severity classification system.

7.5.2 Patient Co-Morbidities and the Influence on Intravenous Antibiotic Therapy

As shown in Table 14 there were very few variables which were statistically significant on univariate analysis in the prospective evaluation of infection severity. Interestingly, none of the documented co-existent illnesses appeared to be associated with intravenous treatment in our prospective study. This lack of association is in sharp contrast to our chart review, where we did identify an association between a chart record of diabetes, peripheral vascular disease or immunocompromise and a decision to treat with intravenous antibiotics.

7.5.3 Explanation of the Discrepancy Between the Chart Review and the Prospective Study

Since the accuracy of chart reviews is heavily dependent on the quality and completeness of the records (and Emergency Department records are notoriously brief and truncated) we have to assume that the numbers of recorded co-morbidities in the chart review may be underestimated. Additionally, the quality of the charting may be biased by the physician's treatment decision. For example, the observed association between these co-morbidities and intravenous antibiotic treatment may, in fact, be an association between the quality of charting for patients treated more aggressively. In other words, physicians leaving a medico-legal record justifying an aggressive therapy may have been more motivated to record the presence of these conditions than physicians who selected a treatment with oral antibiotics.

Another version of this potential bias is that physicians choosing to treat with oral antibiotics may be more judicious in inquiring and documenting the absence of these conditions than those who treated with intravenous antibiotics. Both of these potential biases in the quality of the Emergency Department record could enhance the association between the presence of diabetes, peripheral vascular disease and immunocompromise with intravenous antibiotic therapy observed in our chart review but not in our prospective study.

Finally, the small numbers and the low prevalence of these conditions in our prospective study group may have limited the power of the study to identify this association (a type II error). However, our careful prospective study represents the most concise evaluation of these factors to date.

7.5.4 Infection Features and the Influence on Intravenous Antibiotic Therapy

Our chart review revealed an association between many of the documented features of infection and intravenous treatment. Within our prospective study, only a few of these features were identified as being associated with intravenous treatment: previous (presumably failed) treatment with oral antibiotics, a history of recurrent cellulitis and two of the three manifestations of local or systemic spread (fever and/or the presence of systemic symptoms of infection). Additionally, of the several objective measurements tested, only the size of infection appeared to discriminate between patients treated with oral versus intravenous antibiotics.

The same limitations discussed above apply to this part of the analysis – that is, each part of the study, the chart review and the prospective study, have their own inherent limitations. The potential for bias in the chart review documentation, the slightly

different comparator groups between the two studies and the potentially low power of the prospective study limit any conclusions from being drawn. However, several of these variables have very strong face value or clinical credibility. For example, someone initially treated with an appropriate dose of oral antibiotic that reports clinical worsening of symptoms requires intravenous antibiotic treatment. Also, as previously discussed, using the presence of any of the features of local or systemic spread to justify intravenous antibiotic therapy seems like an appropriate decision.

The critical question here seems to be: does the size of infection, in the absence of any of these clinically credible indicators, influence the decision to administer intravenous antibiotic therapy? Absolute size does appear to be an influence, but there was no highly sensitive or highly specific cut point that currently defines clinical practice. If we look more closely at the mean size between groups, and use those values as trial cut points, we find these values perform poorly as the basis for decisions. For example, the mean size for infections correctly classified as 'mild' was 220cm^2 (compared to a mean size of 640cm^2 in the moderate group). However, using 220cm^2 as a threshold value to define moderate yields a sensitivity of 77% and a specificity of 72%, due to the significant size overlap between the two groups.

7.5.5 The Issue of Circularity and Criterion Contamination

One of the major problems with drawing conclusions from these two preliminary studies (the chart review and the prospective study) is that we are evaluating treatment decisions that were not made in isolation from the clinical indicators of interest. In other words, the physicians making the treatment decisions made all of the measurements and had access to the same information that we used for our analysis. This has the potential

to cause a circular cause and effect, where the final diagnosis (in this case the degree of severity) is predicated on the presence of the characteristics of interest. This has been referred to as criterion contamination, where an artificially high correlation exists between a criterion and an outcome based upon that criterion.⁹¹

While we acknowledge the inherent problems of physicians predicting their own decisions, we again must point out that there are currently no guidelines for evaluating the severity of cellulitis and related skin infections in the Emergency Department. What we have attempted to do, in this first step towards a clinical trial of Emergency Department cellulitis treatment, is define the current landscape. We have provided a snapshot of the reproducible and objective markers that appear to be associated with a physician decision to treat with intravenous antibiotics. We have also identified the areas of decision-making that are not transparent on analysis, such as the impact of the size of the cellulitis on the treatment decision.

7.5.6 Summary

In summary, there was an observed association in our one-year chart review between the presence of diabetes, peripheral vascular disease and immunocompromise and a decision to treat with intravenous therapy. However, our prospective study failed to confirm these associations. There are several possible explanations for this disagreement, including biases in the chart review and a lack of power within the prospective study. The impact of co-morbid disease on infection severity remains unclear. However, this uncertainty justifies the ethical inclusion of patients with co-morbid disease in future clinical trials of cellulitis. Future studies should operationalize the definitions of each co-existent illness, so that these potentially important subgroups

may be identified accurately. Our study also showed an association between prior antibiotic therapy, or the presence of any signs of local or systemic spread, and a decision to treat with intravenous antibiotics.

The mean size of infection was significantly larger in patients treated with intravenous antibiotics, however there was a large overlap between the two groups, even once the other associated characteristics were removed from the analysis. There was no single size cut-off above which all patients were treated with intravenous antibiotics. Since patients with large infections were being treated with oral antibiotics in this observational study, it is ethically justifiable to randomize patients with all sizes of infection in our proposed future clinical trial.

7.6 Identifying Features Predicting Treatment Failure (Objective 5)

Identifying patients who are likely to fail treatment is a critical piece of the puzzle in determining eligibility for a clinical trial. If patients with certain clinical features are more likely to fail on a particular treatment regimen, than it would not be ethical to randomize similar patients to that regimen in a future clinical trial. Our prospective study looked at the first visit characteristics and measurements of all 78 study patients and compared them between the two groups of treatment failures and clinical responders.

The univariate analysis found the mean age in patients who later failed treatment to be significantly older, although the age range between the groups overlapped. Also, patients with documented evidence of peripheral vascular disease were more likely to fail treatment. No other patient characteristics or co-morbidities were significantly different between the two groups.

7.6.1 History of Prior Antibiotics and Treatment Failure

There was a very high proportion of patients in the treatment failure group with a history of previous antibiotic treatment for the infection. These patients were all treated with Emergency Department-based intravenous antibiotics after a (presumably ineffective) course of oral antibiotics. This finding justifies an aggressive approach to this subset of patients: either an admission to hospital or initiation of home intravenous antibiotics, and argues against the inclusion of these patients in a subsequent randomized trial of Emergency Department based intravenous antibiotic therapy.

7.6.2 Olecranon Bursitis and Treatment Failure

Another interesting finding is the high proportion of olecranon bursitis patients in the treatment failure group. Although there were only a few of these patients in the study population, the failure rate in this group was high (40%) when compared to the overall failure rate of 18%. Olecranon bursitis appears to be another important subgroup with a high rate of subsequent incision and drainage, intravenous antibiotic treatment failure and admission to hospital. Again, a strong argument could be made to exclude patients with olecranon bursitis from randomization in a future clinical trial.

7.7 Progress Toward a Clinical Trial

Many of the questions addressed in this thesis will not be answered definitively until a randomized trial of cellulitis treatment in the Emergency Department has been performed. The work completed here represents the first in a series of steps toward the eventual goal of such a trial. The final section of discussion will summarize the design and methods of this trial, incorporating the results of the thesis.

7.7.1 Clinical Trial Objectives

- 1) *Primary Objective:* To directly compare the efficacy of two antibiotic regimens (once daily intravenous cefazolin versus a single intravenous dose of cefazolin followed by oral antibiotics four times per day) for the treatment of uncomplicated skin and soft tissue infections, as measured through the rate of clinical response. The null hypothesis of this trial is that intravenous antibiotics are superior to oral antibiotics: that is, multiple dose intravenous cefazolin will have a higher rate of clinical response than single dose intravenous cefazolin followed by multiple dose oral cephalexin.
- 2) *Secondary Objective:* To examine the effect of several other clinical and demographic characteristics on the rate of clinical response to antibiotic therapy. The null hypothesis of this trial is that age, underlying medical illness, type of infection and size of infected area have no effect on the rate of clinical response to antibiotics.

7.7.2 Design, Setting and Interventions

This will be a double-blinded (i.e. blinded to patients and health care providers) randomized controlled trial with two study groups: a) multiple dose intravenous cefazolin and b) single dose intravenous cefazolin followed by oral cephalexin. Randomization will be simple and not stratified or blocked. It will be run at two centres (Kingston and Ottawa, Ontario) with four hospital sites and Emergency Departments: Kingston General Hospital and Hotel Dieu Hospital, and the Ottawa Hospital (Civic and General Campuses). This trial has been designed as an equivalence trial. As such, the null hypothesis of this trial is that multiple dose intravenous cefazolin will be superior to single dose intravenous cefazolin followed by multiple dose oral cephalexin.⁸⁹

7.7.3 Inclusion Criteria

Patients eligible for inclusion will have at least three of the following signs and symptoms clearly caused by infection: local erythema, induration, pain, warmth, drainage, lymphangitis, fever of 38°C or greater, and systemic symptoms of infection (including but not limited to nausea, vomiting, malaise, and myalgias). These symptoms will have been present for no longer than one week. Abscesses with greater than one centimeter of surrounding erythema and/or signs of lymphangitis will also be eligible for entry after incision and drainage of the abscess. In summary, patients with new onset of signs and symptoms consistent with cellulitis, erysipelas and/or non-surgical wound infection will comprise the study population.

7.7.4 Exclusion Criteria

Patients with signs and symptoms consistent with necrotizing fasciitis will not be eligible. These include severe pain (out of proportion to the observed physical signs of infection), marked systemic signs of infection and inflammation and/or necrosis of the overlying skin with septic shock and circulatory collapse. The following groups of patients will be excluded: children less than 16 years old, pregnant women or breast-feeding mothers, neutropenic or immunocompromised patients. Patients will also be excluded if they are suspected to have any of the following complicated skin and soft tissue infections: infection of an animal or human bite wound, underlying osteomyelitis, infection arising from diabetic foot ulcers or decubitus ulcers, or deep venous obstruction (ultrasound confirmation of deep venous thrombosis). Patients with allergy to cephalosporin antibiotics, and anaphylactic allergy to penicillin antibiotics will be excluded.

In addition, based on the association with treatment failure documented in this thesis, patients who report prior unsuccessful treatment with oral antibiotics or those who have olecranon bursitis will be excluded from randomization.

7.7.5 Consent

Written, informed consent will be sought from all eligible patients. It will be stressed to all patients that the quality of their medical care will not be influenced by their decision to participate in the trial, and that they may feel free to withdraw at any time. Consent will be voluntary and not coerced. Patients who agree to enter will not be financially compensated. This trial will be submitted to the ethics review board at Queen's University and the University of Ottawa for approval prior to initiation.

7.7.6 Registration and Randomization:

The trial will use a simple randomization scheme, carried out according to the following instructions: All eligible patients will have their names, hospital identifying number and clinical diagnosis entered in a logbook stored in each Emergency Department. Patients who consent to be randomized will have their consent recorded in the Emergency Department log, and the pharmacy will be contacted. The hospital pharmacy will have drug packages for each study arm ready, prepared according to a randomization list. This list will be created through a computer-generated random number sequence and will randomize patients to daily intravenous cefazolin or oral cephalexin (see below), following an initial single (unblinded) dose of intravenous cefazolin. The hospital pharmacy will assign the patient a study identification number, which will be entered in an Emergency Department logbook. The hospital pharmacy will record the patient name, study identification number and treatment assignment in a

separate pharmacy log. Patients, study personnel and treating physicians will be blinded to the treatment assignment.

7.7.7 Treatment Schedules

After recruitment, randomization and initiation of treatment (first dose of intravenous cefazolin) they will return to the Emergency Department daily for re-evaluation and administration of medication. They will receive antibiotics according to one of the following treatment schedules:

- A) Cefazolin (Ancef) 2 grams IV co-administered with 1 gram probenecid orally, once daily in the Emergency Department. Oral antibiotic placebo will be taken four times daily on an outpatient basis.
- B) Cephalexin (Keflex) 500 mg po four times daily as an outpatient. Intravenous placebo with probenecid placebo will be given once daily in the Emergency Department.

All placebo drugs will be physically indistinguishable from their active counterparts, so that the double-blind nature of the study will be maintained.

All entered patients will receive daily evaluation in the Emergency Department and will be classified as either "clinical responders" or "treatment failures." "Clinical responders" will be discharged from daily Emergency Department evaluation and switched to oral cephalexin therapy, 500 mg four times daily (unblinded). "Treatment failures" will be entered into the home intravenous therapy program to receive unblinded intravenous antibiotics or admitted to hospital for further assessment and inpatient treatment. Further evaluation, specialist consultation and surgical intervention in these patients will occur at the discretion of the Emergency Department attending physician.

All study patients will receive a minimum of ten days of antibiotic therapy, and will be followed by telephone or in hospital until complete resolution of symptoms has occurred.

7.7.8 Data Collection

Study patients will have the following information collected: demographic data, co-morbid disease (specifically a history of diabetes or peripheral vascular disease), a history of previous cellulitis (including location and treatment), and the history of the infection (timing and duration of symptoms, antecedent cause, etc.) Initial assessment will also include documentation of any symptoms or physical signs of peripheral vascular disease and a urine dip for glucosuria. Positive urine screens will be followed by a single random serum blood sugar. The presence of symptoms or physical signs of peripheral vascular disease will result in the patient's identification as 'positive' for peripheral vascular disease. A single random blood sugar of greater than 11 mmol/L will result in the patient's identification as 'positive' for diabetes. These ancillary investigations will be performed to ensure that patients with diabetes or peripheral vascular disease are accurately identified at the time of randomization.

Daily evaluations will include documentation of the presence of systemic spread of infection (fever, nausea, vomiting, lymphangitis or local lymphadenopathy), size of infection (both largest diameter and area) and a digital photograph of the infection, taken in a standardized fashion.

7.7.9 Side Effects, Dose Modification and Withdrawals

Patients who develop any signs of allergy to one of the study drugs will be withdrawn from the study and treated with a non-cephalosporin antibiotic. Side effects reported by patients will be recorded, and if these side effects are felt to be intolerable by

the study patient, he or she will also be withdrawn and treated with a non-cephalosporin antibiotic.

7.7.10 Patient Compliance

Oral antibiotics and oral placebo pills will be distributed in blister packaging containing one day's supply of pills. The next day's supply will be administered after the patient has returned to the Emergency Department, for daily clinical evaluation antibiotic therapy. Compliance with oral medication will be assessed through daily pill counts of any leftover blister packaged pills. Patients will be classified as *compliant* (complete compliance with oral medication), *somewhat compliant* (greater than 75% oral medication ingested) or *non-compliant* (less than 75% oral medication ingested).

Intravenous antibiotics will be administered by the Emergency Department study personnel, so compliance with intravenous therapy will be 100% assuming that all entered patients appear for their daily assessments. If patients fail to present to the Emergency Department for an assessment, they will be contacted by telephone and asked to return for re-evaluation.

7.7.11 Outcome Measures: Treatment Failure

The primary outcome measure will be the rates of 'treatment failure' and 'clinical response' in each group. Patients will be labeled as a "treatment failure" if they meet any one of the following five criteria:

- Persistent enlargement of infection size (greater than 10% per day) over two consecutive days of antibiotic treatment. This corresponds to a ratio of 1.2 (size after treatment over initial size).

- Require an incision and drainage procedure, or other surgical intervention, after 48 hours of antibiotic therapy.⁶
- New development of any signs of systemic spread of infection after the initiation of antibiotic treatment (specifically fever, nausea, vomiting, lymphangitis or local lymphadenopathy).
- Lack of resolution of systemic signs of infection (as described above) after two consecutive days (48 hours) of antibiotic therapy.
- Any clinical suspicion of bacteremia or sepsis after the initiation of treatment (specifically, but not limited to, tachycardia and hypotension).

7.7.12 Outcome Measures: Clinical Responders

Patients will be labeled as “clinical responders” when they have satisfied both of the criteria below:

- Absence of any of the signs of systemic infection spread for three consecutive days (fever, nausea, vomiting, lymphangitis, local lymphadenopathy) **and**
- Decrease in infection size of 10% per day for three consecutive days. This corresponds to a ratio of 0.7 (size after treatment over initial size).

7.7.13 Secondary Treatment Failures

Patients whose infections recur or worsen after being discharged from the study protocol will be labeled “secondary treatment failures.” These secondary treatment failures will be entered into the home intravenous program, and treated in exactly the same manner as primary treatment failures. ‘Secondary treatment failures’ will be presumed to have occurred through noncompliance of medication *after discharge* from

regular Emergency Department evaluation. This situation is expected to occur in only a very small number of patients.

7.7.14 Protocol Violations:

Patients who are ineligible, as defined by patients with clear exclusion criteria randomized in error or by un-randomized patients mistakenly included in the trial, will be excluded from analysis. The numbers of ineligible patients and reasons for ineligibility will be documented.

Protocol violations or study withdrawals will continue to be followed until their infection is completely healed. Reasons for the withdrawal or type of protocol violation will be recorded. Patients will be analyzed both on an 'intent-to-treat' basis (including all withdrawals and protocol violations) and on a per protocol basis (excluding all patients who are not treated exactly as specified).

7.7.15 Sample Size and Estimated Time to Accrual:

The sample size for this trial has been calculated as 423 patients per study group. The rate of recruitment for the prospective study in this thesis was 80 episodes of infection in eight months, and the recruitment of a similar pilot study in one Ottawa centre was 32 episodes in five months. Assuming a similar rate of recruitment at the second Ottawa centre, the total estimated monthly recruitment rate is 22 episodes per month. On this basis, we estimate the time to accrual as approximately 40 months.

7.7.16 Statistical Analysis:

The null hypothesis of this trial is that intravenous antibiotics are clinically superior to oral antibiotics in the treatment of uncomplicated skin and soft tissue infections, as manifested by a rate of at least 10% more clinical responders in the

intravenous treatment group. The primary outcome measure, the percentage of clinical responders and treatment failures for each treatment group, will be calculated with 95% confidence intervals. The between treatment difference (i.e. difference between the rate of clinical responders in the intravenous group and the oral group) will also be calculated, with a 95% confidence interval. If the 95% confidence interval for the treatment difference lies entirely within the range of $\pm \Delta$, or in this trial $\pm 10\%$, then the treatments may be declared equal.⁸⁹ Both an intent-to-treat and a per protocol strategy (as previously described) will be used in the analysis, so this calculation will be performed twice. This will allow some idea as to the strength of any declaration of equivalence.

The two treatment groups will be analyzed in terms of baseline demographics and infection type, to assess the adequacy of the randomization procedure in balancing the treatment groups. The time to clinical improvement and the incidence and types of side effects and complications between the two groups will also be compared. Differences between treatment groups will be evaluated using a Chi-square statistic for categorical variables (such as percentage of patients with side effects), and means of continuous variables (such as time to improvement) will be compared using parametric or non-parametric statistics where appropriate. The effect of pre-existing medical conditions, age, prior significant cellulitis, type of infection, location of infection and compliance with adjuvant therapy on therapeutic response will be evaluated using a multiple logistic model.

8. Conclusions

This thesis project has accomplished a number of goals. A sample size and trial protocol for a clinical trial comparing Emergency Department-based intravenous antibiotic with outpatient oral antibiotics for patients with cellulitis has been developed. Several objective measurements were developed, *de novo*, and then prospectively tested on a group of 78 Emergency Department patients. These measurements were systematically examined for their inter-rater reliability, feasibility and criterion validity (in comparison to a gold standard derived from physician treatment decisions). Of all of the measurements, only the size of infection, and change in size over time, achieved statistical significance in all three domains. The measurements that performed well were incorporated into the trial protocol as the primary outcome measurement, and used in defining treatment failure.

This study also failed to demonstrate an association between other significant health conditions and infection severity (as perceived by the treating Emergency Physicians). The link between co-morbidities and infection severity requires further research, however, this lack of association allows the ethical randomization of patients with these characteristics into our proposed trial. Our study also failed to identify a size that clearly demarcates severity. There was considerable overlap between the size of infection and the choice of antibiotic treatment, suggesting that there is some clinical equipoise regarding the most appropriate route of antibiotics for patients with large infections. Once again, we can now ethically randomize patients with all sizes of infection to a clinical trial of oral and intravenous antibiotics.

Finally, the study identified an association between prior antibiotic treatment, and subsequent treatment failure with Emergency Department-based intravenous antibiotics. A similar association, although less robust, was identified between olecranon bursitis (a subtype of cellulitis involving the elbow, frequently complicated by soft tissue abscess) and subsequent treatment failure. Based on this association, patients with these characteristics should be excluded from eligibility in the proposed clinical trial.

By identifying and overcoming several of the barriers to a clinical trial of Emergency Department cellulitis therapy we have set the stage for the performance of this trial. Once this trial has been performed we will be able to define and improve both the resources and patient outcomes associated with the practice of Emergency Department-based intravenous antibiotics.

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Table 1: Reasons for Exclusion

Reason for exclusion	Number of patients
Direct referral to specialty service	46
No evidence of skin infection	48
No record of visit	9
<i>Age < 15</i>	43
Other infectious diagnosis:	177
Bite wound infections	32
Post-operative infections	18
<i>Paronychia or ingrown toenail</i>	104
Infected ulcers	17
Septic joints	3
Necrotizing fasciitis	3
Total	323

Table 2(a): Characteristics and Co-Morbidities of 426 Emergency Department Visits with Skin and Soft Tissue Infections

	Total Patients (n=426)	Cellulitis (n=174)	Wound Infection (n=72)	Erysipelas (n=25)	Abscess (n=155)
Mean Age (SD)	45.1 (18.1)	48.4 (13.7)	48.0 (18.2)	51.8 (13.7)	38.9(15.2)
Age Range in Years	15-93	16-93	15-88	15-70	15-81
Co-morbidities (%):					
Peripheral Vascular Disease	0.7	1.7	0	0	0
Diabetes Mellitus	8.9	5.2	6.9	12.0	6.5
Immunocompromised	1.9	2.8	0	4.0	1.3
Known Malignancy	2.1	4.6	0	4.0	0
Intravenous Drug Abuse	7.5	10.9	1.4	0	8.4

Table 2(b): Specific Features and Management of 445 Skin and Soft Tissue Infections in 426 Emergency Department Patients

	Total Patients (n=445)	Cellulitis (n=186)	Wound Infection (n=72)	Erysipelas (n=26)	Abscess (n=161)
Investigations (%):					
White Blood Count Performed	18.0	31.2	11.1	23.1	5.0
White Blood Count > 10 x 10 ⁵	9.4	15.6	4.2	19.2	3.1
Blood Culture Drawn	16.0	24.7	9.7	7.7	9.9
Growth Observed on Blood Culture	1.8	3.8	0	0	0.6
Management (%):					
No or Topical Antibiotics	14.4	0	2.8	0	39.8
Oral Antibiotics	47.4	45.2	59.7	19.2	48.4
Intravenous Antibiotics	38.2	55.9	37.5	84.6	10.6
Consultation	11.0	20.4	2.8	0	5.6
Admission	7.4	15.6	1.4	0	1.9

Table 3(a): Patient Characteristics and Co-Morbidities Associated with Intravenous Antibiotic Therapy in the 367 Study Patients Who Received Antibiotics

Variable	Intravenous Antibiotics (n =165)	Oral Antibiotics (n =202)	Significance
Male Gender	54.1	57.5	NS
Mean Age (SD)	48.7 (18.2)	42.6 (17.5)	NS
Co-Morbidities:			
Intravenous drug use	9.1	7.9	NS
Diabetes mellitus	12.7	6.9	0.04
Peripheral vascular disease	1.8	0	0.09
Immunocompromised	3.6	0.5	0.05

Table 3(b): Infection Features Associated with Intravenous Antibiotic Therapy in the 379 Episodes of Infection Treated with Antibiotics

Variable	Intravenous Antibiotics (n =170)	Oral Antibiotics (n =209)	Significance
Features of Infection:			
History of fever	15.9	4.3	<0.01
History of chills	10.0	2.9	<0.01
History of nausea	2.4	0.5	NS
History of vomiting	2.4	0	0.04
History of myalgias	1.8	0.1	NS
Previous Antibiotics	20.5	8.1	<0.01
Lymphadenopathy or lymphangitis	18.8	9.6	0.01
Fever in Emergency Department	10.6	3.3	0.01
White blood count > 10×10^5	11.1	0	<0.01
Location of infection:			
Head Neck	17.1	18.7	NS
Arm	18.8	20.1	NS
Hand	11.2	16.7	NS
Trunk	2.4	9.6	<0.01
Leg	34.1	25.4	0.06
Foot	16.4	9.0	0.03

Table 4(a): Patient Characteristics Across the Three Study Populations

Patient Characteristics	Entire Study Sample (n=78)	Interobserver Substudy (n=19)	Multiple Visits Substudy (n=49)
Age Range	15-89	27-89	15-89
Mean Age (SD)	49 (19)	57 (21)	49 (19)
<u>Patient Characteristics (%)</u>			
Male	60.3	42.1	57.1
Intravenous Drug Use	7.6	0	8.2
Diabetes Mellitus	6.3	15.8	8.2
Peripheral Vascular Disease	6.3	15.8	8.2
Peripheral Edema	15.2	31.6	20.4
Dermatologic Disorder	10.1	10.5	12.2
Previous Cellulitis	26.6	31.6	32.7

Table 4(b): Infection Characteristics Across the Three Study Populations

Infection Characteristics*	Entire Study Sample (n=80)	Interobserver Substudy (n=19)	Multiple Visits Substudy (n=50)
History of Trauma Prior to Infection	43.8	31.6	34.0
Laceration	12.5	0	6.0
Abrasion Scratch Blister	8.8	10.5	6.0
Puncture Wound	12.5	10.5	10.0
Blunt Trauma (no skin break)	10.0	10.5	12.0
Previous Antibiotic Treatment	22.5	15.8	38.0
Location of Infection			
Head Neck	0.3	0	0
Arm	30.4	15.8	36.0
Hand	6.3	5.3	6.0
Trunk	3.8	0	0
Leg	41.3	36.8	46.0
Foot	16.3	26.3	12.0
Olecranon Bursitis	12.7	10.5	18.0
Abscess at Study Enrollment	13.9	5.3	12.0
Abscess Formation at Any Time	21.5	15.8	22.0
Intravenous Antibiotic Treatment	66.3	73.8	90.0
Admitted to Hospital	12.5	15.8	12.0
Treatment Failure - Required 2 nd Intervention	17.5	15.8	26.0
Incision & Drainage after 1 st Visit	3.8	3	6.0
Change in Antibiotic	7.5	0	12.0
Specialty Consultation after 1 st Visit	7.5	5	12.0
First ED Visit Measurements:			
Fever	25.3	21.1	36.0
Other Systemic Symptoms	27.8	31.6	42.0
Lymphangitis or Lymphadenopathy	26.5	5.3	24.0
Mean Area Erythema (SD)	556 cm ² (655)	468 cm ² (373)	688 cm ² (706)

*Values are expressed as percentage of column total unless otherwise specified

Table 5(a): Agreement Between Physicians for Dichotomous Variables

Variable	++	--	+-	-+	Agreement (%)	Kappa (SE)
Fever	3	16			100	1.0 (0)
Other Systemic Symptoms	4	13	2		90	0.73 (0.17)
Lymphadenopathy/ Lymphangitis		15	1	2	83	-0.09 (0.06)
Admission	1	15		2	89	0.46 (0.31)
Severity (mild moderate severe)	11	2	2	2	76	0.35 (0.26)
Abscess (yes unsure no)	1	16			100	1.0 (0)
Intensity (not or little red/ very red)	16	1			100	1.0 (0)

Table 5(b): Calculated Agreement for the Continuous Inter-Rater Measurements

Measurement	Agreement (%)	ICC (95% CI)
Intensity of erythema	100	0.89 (0.73 – 0.96)
Physician impression of severity	76	0.39 (0.01 – 0.72)
Likelihood of abscess	100	0.81 (0.55 – 0.92)
Surface temperature (within 1°C)	82	0.90 (0.82 – 0.94)
Diameter erythema (within 2 cm)	87	0.98 (0.96 – 0.99)
VAS Pain (within 1 cm)	79	0.95 (0.84 – 0.99)

Table 6(a): Demographics Features of Patients Within Multiple Visits Substudy and Those With Data Recorded from Only One Visit

Patient Characteristics	Multiple Visits Substudy (n=49)	Only Single Visit Data (n=29)	Significance
Age Range	15- 89	15- 82	NS
Mean Age (SD)	49 (19)	47 (18)	
<u>Patient Characteristics (%):</u>			
Male	57.1	65.6	NS
Intravenous Drug Use	8.2	0	NS
Diabetes Mellitus	8.2	6.9	NS
Peripheral Vascular Disease	8.2	6.9	NS
Peripheral Edema	20.4	6.9	NS
Dermatologic Disorder	12.2	3.4	NS
Previous Cellulitis	32.7	17.2	NS

Table 6(b): Comparison of Infection Features Between Infections Included in Multiple Visit Substudy and Those with Data from Only One Visit

Infection Characteristics	Multiple Visits Substudy (%) N = 50	Only Single Visit Data (%) N=30	Significance
History of Trauma Prior to Infection	34.0	60.0	0.04
Laceration	6.0	23.3	
Abrasion/Scratch/Blister	6.0	13.3	
Puncture Wound	10.0	16.7	
Blunt Trauma (no skin break)	12.0	6.7	
Previous Antibiotic Treatment	38.0	24.0	NS
Location of Infection:			
Head Neck	0	13.3	
Arm	36.0	23.3	
Hand	6.0	6.7	
Trunk	0	10.0	
Leg	46.0	33.3	
Foot	12.0	23.3	
Olecranon Bursitis	18.0	3.3	<0.01
Abscess at Study Enrollment	12.0	16.7	NS
Abscess Formation at Any Time	22.0	20.0	NS
Intravenous Antibiotic Treatment	90.0	26.7	<0.01
Admitted to Hospital	12.0	13.3	NS
First ED Visit Measurements:			
Fever	36.0	6.7	<0.01
Other Systemic Symptoms	42.0	3.3	<0.01
Lymphangitis or Lymphadenopathy	24.0	30.0	NS
Mean Area Erythema in cm ² (SD)	688 (708)	335 (494)	0.01

Table 7: Number of Days of Emergency Department Treatment in the 50 Episodes of Infection (Multiple Visit Substudy)

Days of Treatment:	Treatment Failure (n=13)	Clinical Responder (n=37)	Total
2	4 (31%)	17 (46%)	21
3	3 (23%)	11 (30%)	14
4	3 (23%)	5 (14%)	8
≥ 5	3 (23%)	4 (11%)	7

Table 8: Type of Second Treatment Intervention and Day of Intervention in the 13 Treatment Failure Patients (total is > 13 since some patients had >1 intervention)

Treatment Failure Patients (n = 13)	Day 2	Day 3	Day 4	Day 5	After Day 5	Total
I&D Performed	2	1				3
Change in Antibiotic	3	1		1	1	6
Consultation					1	1
Admission	4	1				5
Home IV Therapy Initiated		1				1
Total	9	4		1	2	16

Table 9: Comparing Symptoms in "Clinical Responders" versus "Treatment Failures"

Symptom	Day 1 (n = 37)	(n = 13)	
	Clinical Responder (%)	Treatment Failure (%)	Significance
Fever	36.1	41.7	0.74
Other Systemic Symptom	41.7	46.2	0.78
Lymphangitis or Lymphadenopathy	20.6	41.7	0.25
Any of Above	54.1	61.5	0.71
Symptom	Day 2 (n = 26)	(n = 12)	
	Clinical Responder (%)	Treatment Failure (%)	Significance
Fever	28.6	25.0	1.0
Other Systemic Symptom	35.7	31.7	0.74
Lymphangitis or Lymphadenopathy	34.6	33.3	0.94
Any of Above	48.6	53.8	0.30
Symptom	Day 3 (n = 21)	(n = 7)	
	Clinical Responder (%)	Treatment Failure (%)	Significance
Fever	9.5	28.6	0.25
Other Systemic Symptom	19.0	57.1	0.14
Lymphangitis or Lymphadenopathy	28.6	40.0	0.85
Any of Above	47.6	71.4	0.40

Table 10: Comparing Mean Measurements of Infection Characteristics Between “Clinical Responders” and “Treatment Failures” During Treatment Days One to Three

	Clinical Responder (mean values)	Treatment Failure (mean values)	Significance
Measurement	Day 1 (n = 36)	(n = 13)	
Largest Diameter Erythema (cm)	25.8	31.3	NS
Area Erythema (cm ²)	565	1030	NS
Temperature Difference (°C)	3.3	3.8	NS
Intensity of Erythema (1-5)*	3.6	3.8	NS
Patient Pain (1-10)**	5.1	3.1	0.05
Measurement	Day 2 (n = 28)	(n = 12)	
Largest Diameter Erythema (cm)	27.2	41.0	0.01
Area Erythema (cm ²)	565	1205	0.05
Temperature Difference (°C)	2.7	3.0	NS
Intensity of Erythema (1-5)*	3.3	3.5	NS
Patient Pain (1-10)**	3.6	3.5	NS
Measurement	Day 3 (n = 21)	(n = 7)	
Largest Diameter Erythema (cm)	20.3	42.4	0.04
Area Erythema (cm ²)	348	1398	<0.01
Temperature Difference (°C)	1.9	3.2	0.15
Intensity of Erythema (1-5)	3.0	3.3	NS
Patient Pain (1-10)	2.4	3.0	NS

* Intensity of Erythema is measured on a 5 point ordinal rating scale (1 = not red, 5 = very red)

** Patient Pain is measured on a Visual Analogue Scale (0 = no pain, 10 = maximum pain)

Table 11(a): Comparing the Change in the Size of Erythema Between Clinical Responders and Treatment Failures. Using Mean Slopes and Ratio of Size from First to Last Visit

	Clinical Responder <i>Mean</i>	Treatment Failure <i>Mean</i>	Significance
Slope (Area Erythema)	-139.75	230.23	<0.01
Slope (Largest Diameter Erythema)	-38.45	71.93	<0.01
Ratio (Area Erythema)	0.80	2.37	<0.01
Ratio (Largest Diameter Erythema)	0.86	1.50	<0.01

Table 11(b): Testing the Assumption of Normality for the Slope and Ratio Variables

Clinical Improvers	Skewness	SE	Ratio Skewness: SE	Normality Hypothesis Accepted (Y/N)
Slope Area	-2.20	0.39	-5.67	No
Slope Diameter	-2.78	0.39	-7.16	No
Ratio Area	0.47	0.39	1.21	Yes
Ratio Diameter	0.62	0.39	1.60	Yes
Treatment Failures				
Slope Area	1.05	0.62	1.70	Yes
Slope Diameter	1.39	0.62	2.25	No
Ratio Area	2.28	0.62	3.69	No
Ratio Diameter	-0.66	0.62	-0.11	Yes
Clinical Improvers	Kurtosis	SE	Ratio Kurtosis: SE	Normality Hypothesis Accepted (Y/N)
Slope Area	5.89	0.76	7.75	No
Slope Diameter	8.81	0.76	11.61	No
Ratio Area	-0.15	0.76	-0.19	Yes
Ratio Diameter	1.20	0.76	1.57	Yes
Treatment Failures				
Slope Area	2.37	1.19	1.99	Yes
Slope Diameter	3.19	1.19	2.67	No
Ratio Area	5.15	1.19	4.32	No
Ratio Diameter	1.20	1.19	1.40	Yes

Table 12: Comparing Mean Measurements of Physician and Patient Impressions Between "Clinical Responders" and "Treatment Failures" During Treatment Days One to Three

	Clinical Responder (mean values)	Treatment Failure (mean values)	Significance
Measurement	Day 1 (n = 36)	(n = 13)	
Physician Impression of Severity (1-5) ^Ω	2.8	3.0	NS
Patient Impression of Improvement (1-5) ^Ψ	4.1	4.0	NS
Measurement	Day 2 (n = 28)	(n = 13)	
Physician Impression of Severity (1-5) ^Ω	3.0	2.8	NS
Patient Impression of Improvement (1-5) ^Ψ	2.5	2.9	NS
Measurement	Day 3 (n = 21)	(n = 13)	
Physician Impression of Severity (1-5) ^Ω	3.6	2.8	0.01
Patient Impression of Improvement (1-5) ^Ψ	1.8	2.8	0.02

^Ω Physician Impression of Severity is measured on a 5 point rating scale (1 = very severe, 5 = very mild)

^Ψ Patient Impression of Improvement is measured on a Likert Scale, based on agreement with the statement "my infection is better than yesterday" (1 = strongly agree, 5 = strongly disagree)

Table 13(a): Summary of Testing for the Measurements Representing the Clinical Manifestations of Infection

Clinical Manifestation of Infection	Criterion Validity	Reliability	Feasibility	Overall
Absolute Size of Infection:				
Area	-	-	-	Good
Diameter	-	-	-	Good
Change in Size of Infection:				
Ratio	-	-	-	Good
Slope	-	-	-	Good
Temperature Difference	~	-	-	Fair
Patient Pain	~	-	-	Good
Intensity of Erythema	-	-	-	Poor
Physician Impression of Severity	~	~	~	Fair
Patient Impression of Severity	~	~	~	Fair

Legend:

- statistically and clinically performed well
- ~ trend toward good performance (inadequate sample size)
- statistically and clinically performed poorly

Table 13(b): Summary of Testing for the Measurements Representing the Manifestations of Local or Systemic Spread of Infection

Manifestations of Local or Systemic Spread of Infection	Criterion Validity	Reliability	Feasibility	Overall
Fever	~	-	-	Good
Systemic Symptoms	~	~	-	Fair
Lymphangitis	~	~	-	Fair

Table 14: Comparison of Clinical Characteristics Between Mild Infections and Moderate Infections

First Visit Characteristics	Mild (n=27)	Moderate (n=37)	Significance
Male Gender	48.1	62.2	NS
Mean Age (SD)	44.5 (17.3)	46.5 (18.5)	NS
Co-morbidities:			
Intravenous Drug Abuse	7.4	10.8	NS
Diabetes	3.7	8.1	NS
Peripheral Vascular Disease	3.7	8.1	NS
Peripheral Edema	3.7	16.2	NS
Dermatologic Disorder	7.4	10.8	NS
History of Previous Cellulitis	7.4	32.4	0.02
Features of Infection:			
Previous Antibiotic Treatment	7.4	27.0	0.05
Olecranon Bursitis	7.4	10.8	NS
Post-Traumatic Infection	59.3	40.5	NS
Abscess	14.8	10.8	NS
Fever in Emergency Department	11.1	31.4	0.06
Other Systemic Symptoms	3.7	38.9	<0.01
Lymphadenopathy	33.3	24.2	NS
Lymphangitis			
Location of Infection:			
Head Neck	3.7	0	NS
Arm	33.3	27.0	NS
Hand	7.4	5.4	NS
Trunk	7.4	2.7	NS
Leg	29.6	48.6	NS
Foot	18.5	16.2	NS
Measurements of Infection:			
Mean Area in cm ² (SD)	219.9 (213.2)	637.7 (559.2)	<0.001
Mean Largest Diameter	16.3 (10.2)	27.3 (13.4)	<0.001
Erythema (SD)			
Mean Temperature Difference °C (SD)	2.8 (2.1)	3.0 (1.6)	NS
Mean Intensity of Erythema* (SD)	3.3 (0.7)	3.6 (0.7)	NS
Mean Patient VAS Pain (SD)	4.2 (2.2)	5.2 (2.7)	NS

* Intensity of Erythema is measured on a 5 point ordinal rating scale (1 = not red, 5 = very red)

Table 15(a): Comparing Patient Characteristics of Clinical Responders to Treatment Failures

	Clinical Responders N = 64	Treatment Failure N = 14	Significance
Age Range	15 - 89	32 - 82	
Mean Age (SD)	46 (19)	59 (17)	0.02
<u>Patient Characteristics (%):</u>			
Male	59.1	57.1	NS
Intravenous Drug Use	9.1	0	NS
Diabetes Mellitus	6.1	14.3	NS
Peripheral Vascular Disease	4.5	21.4	0.06
Peripheral Edema	13.6	21.4	NS
Dermatologic Disorder	9.1	7.1	NS
Previous Cellulitis	24.2	35.7	NS

Table 15(b): Comparing First Visit Infection Characteristics of Clinical Responders to Treatment Failures

	Responded to Treatment (N = 66)	Treatment Failure (N = 14)	Significance*
History of Trauma Prior to Infection (%)	47.0	28.6	NS
Laceration	12.1	14.3	NS
Abrasion Scratch Blister	13.6	7.1	NS
Puncture Wound	10.6		NS
Blunt Trauma (no skin break)	10.6	7.1	NS
Previous Antibiotic Treatment (%)	16.7	50.0	0.01
<u>Location of Infection:</u>			
Head Neck (%)	1.5	0	NS
Arm (%)	30.3	35.7	NS
Hand (%)	6.1	7.1	NS
Trunk (%)	4.5	0	NS
Leg (%)	39.4	50.0	NS
Foot (%)	18.2	7.1	0.10
Olecranon Bursitis (%)	9.1	28.6	0.05
Abscess at Study Enrollment (%)	12.1	21.4	NS
Intravenous Antibiotic Treatment (%)	59.1	85.7	0.06
<u>First ED Visit Measurements:</u>			
Fever (%)	25.0	33.3	NS
Other Systemic Symptoms (%)	25.0	46.2	NS
Lymphangitis or Lymphadenopathy (%)	27.0	33.3	NS
Mean Area Erythema (SD)	101.5 (110)	465.1 (487)	<0.01

* Significance was reported as NS or Not Significant if the calculated p-values were higher than 0.10

Figure 1: Flow Chart of Patient Enrollment, Treatment Decisions and Outcomes for Prospective Study Patients

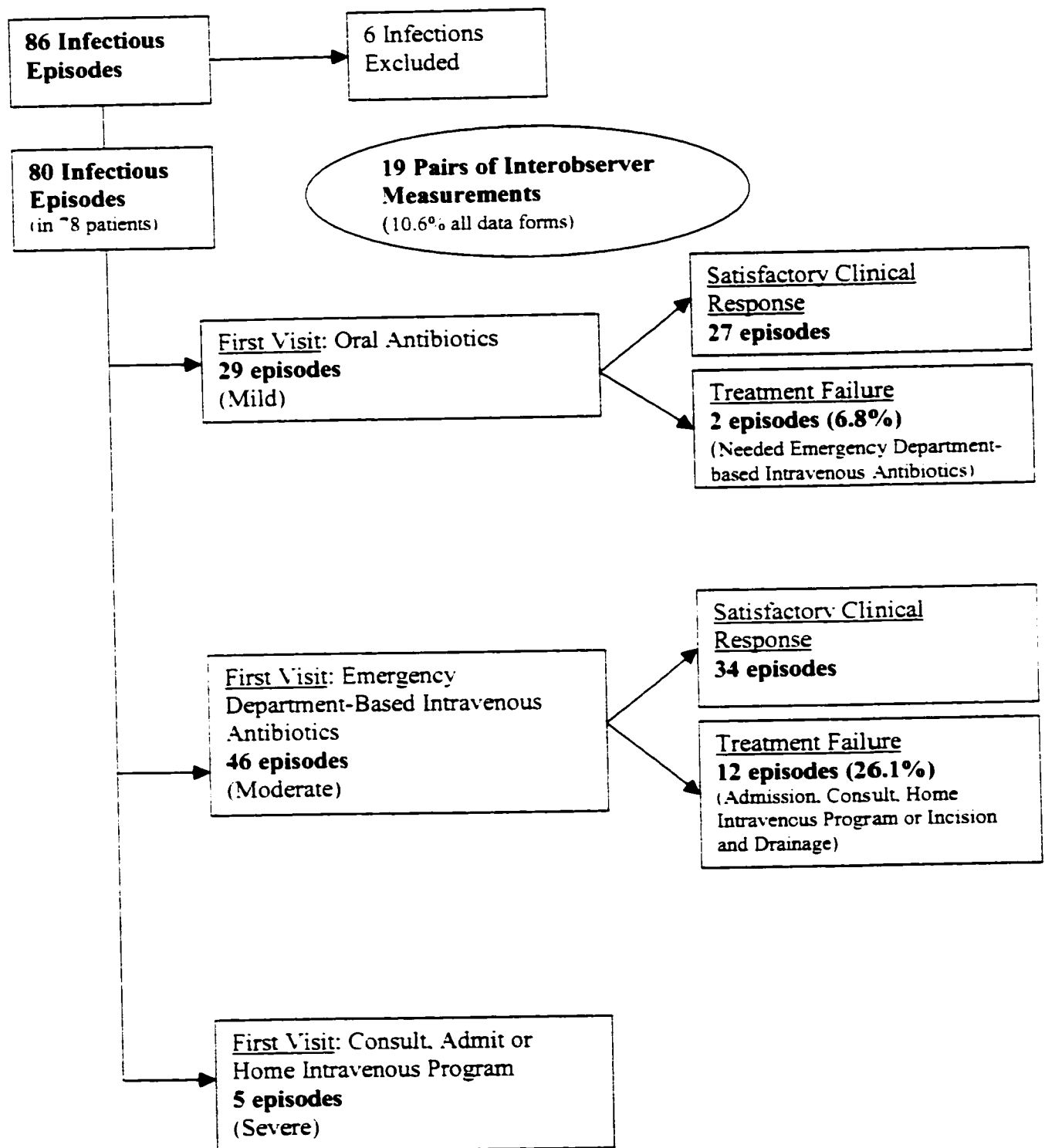


Figure 2(a): Boxplot Comparing the Area of Erythema in the Clinical Responder Group During the First Three Treatment Days

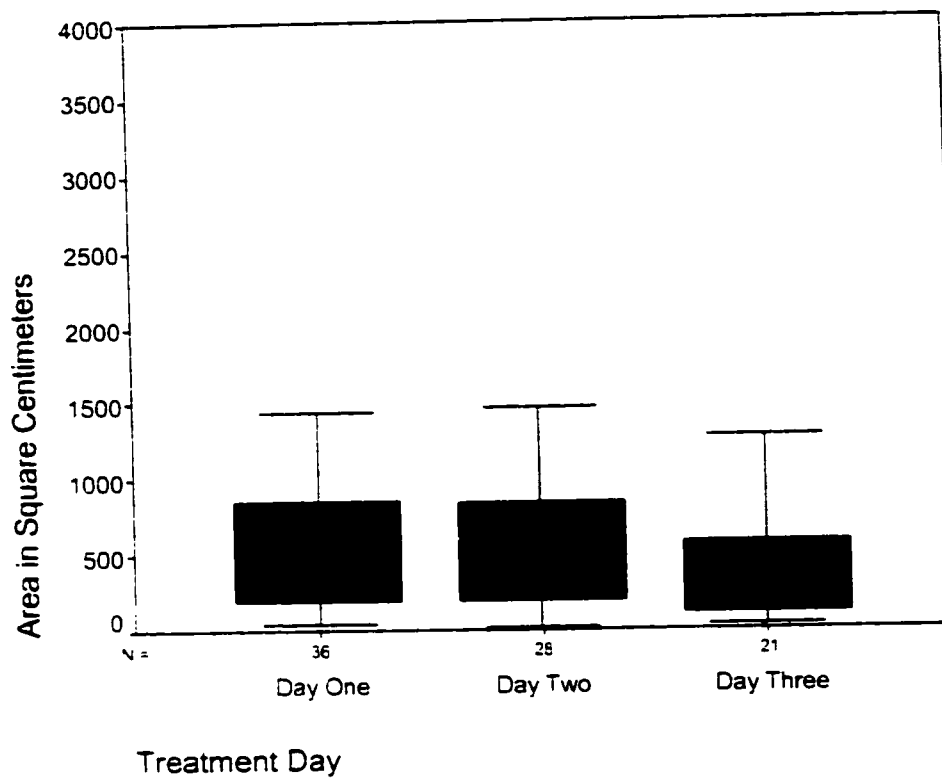


Figure 2(b): Boxplot Comparing the Area of Erythema in the Treatment Failure Group During the First Three Treatment Days

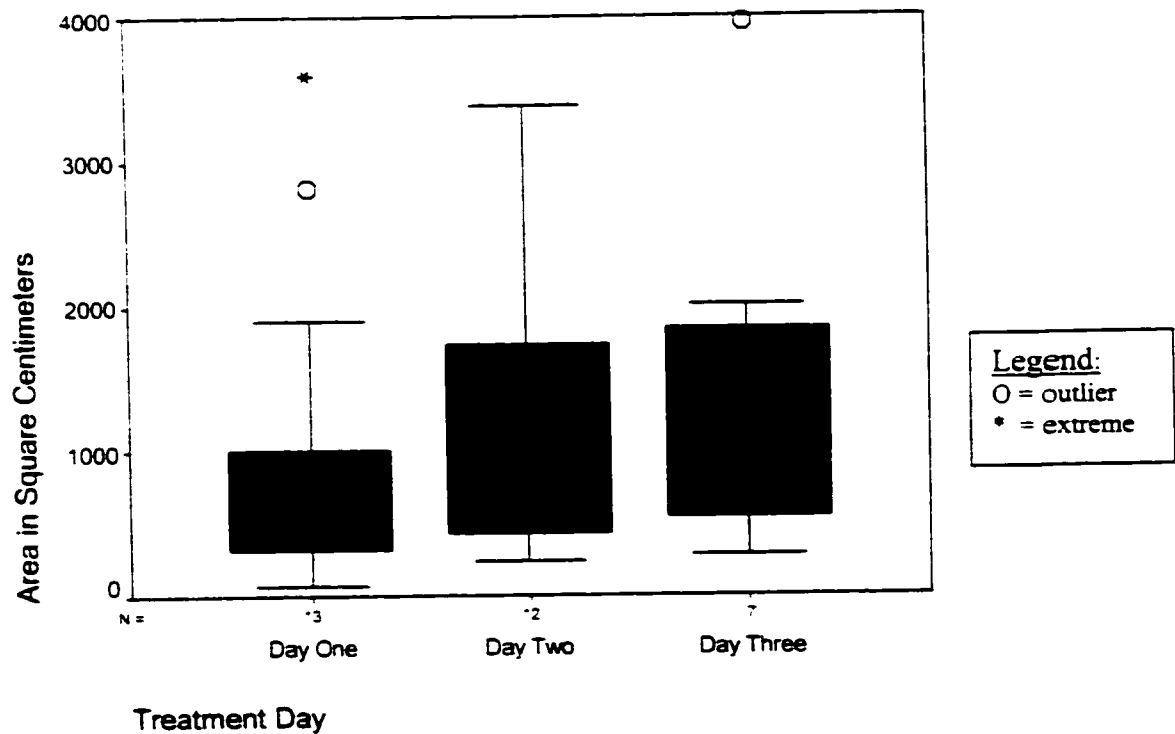


Figure 3(a): Boxplot Showing the Largest Diameter of Erythema (in Centimeters) in the Clinical Responder Group During the First Three Treatment Days

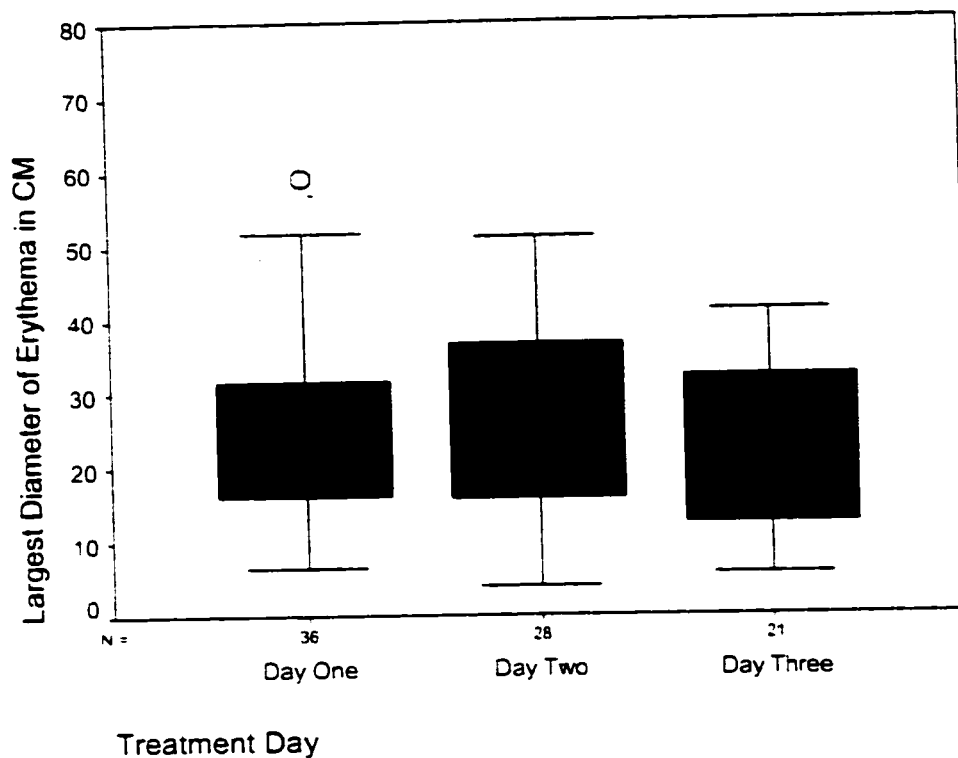


Figure 3(b): Boxplot Showing the Largest Diameter of Erythema (in Centimeters) in the Treatment Failure Group During the First Three Treatment Days

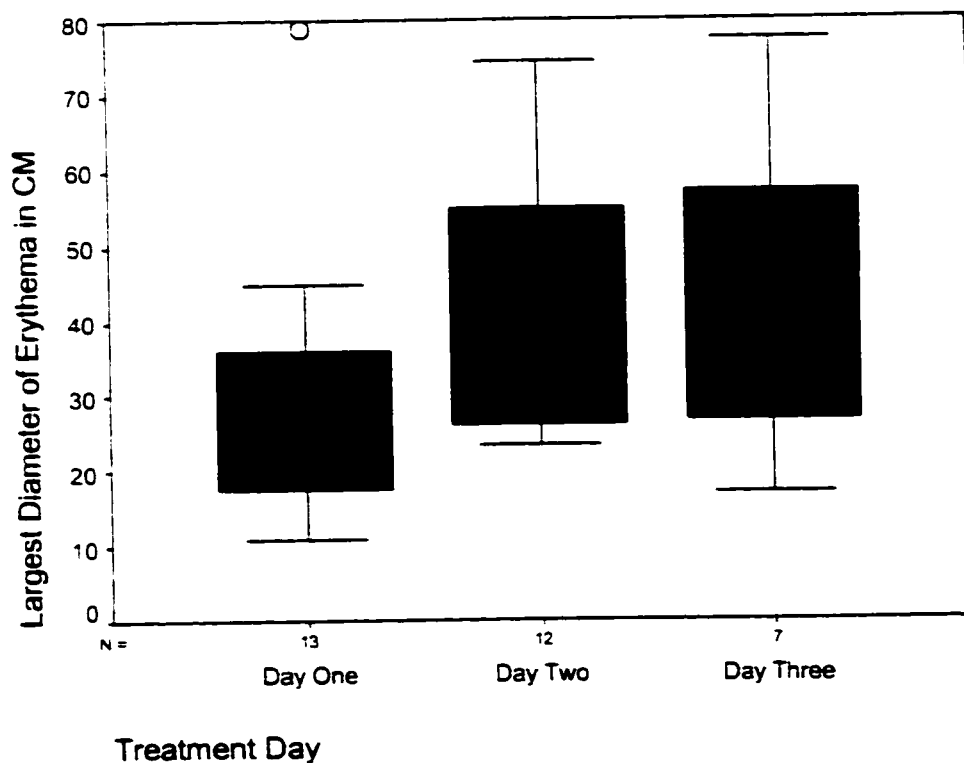


Figure 4(a): Temperature Difference Between Infected and Uninfected Skin During the First Three Days of Treatment in the Clinical Responder Group

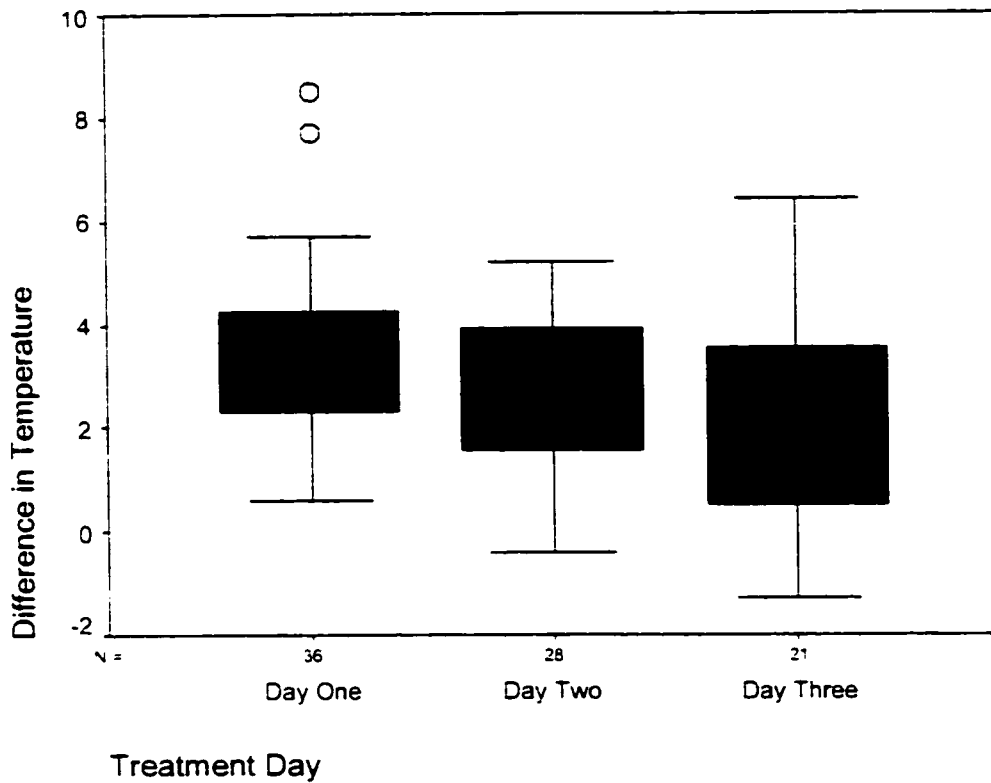


Figure 4(b): Temperature Difference Between Infected and Uninfected Skin During the First Three Days of Treatment in the Treatment Failure Group

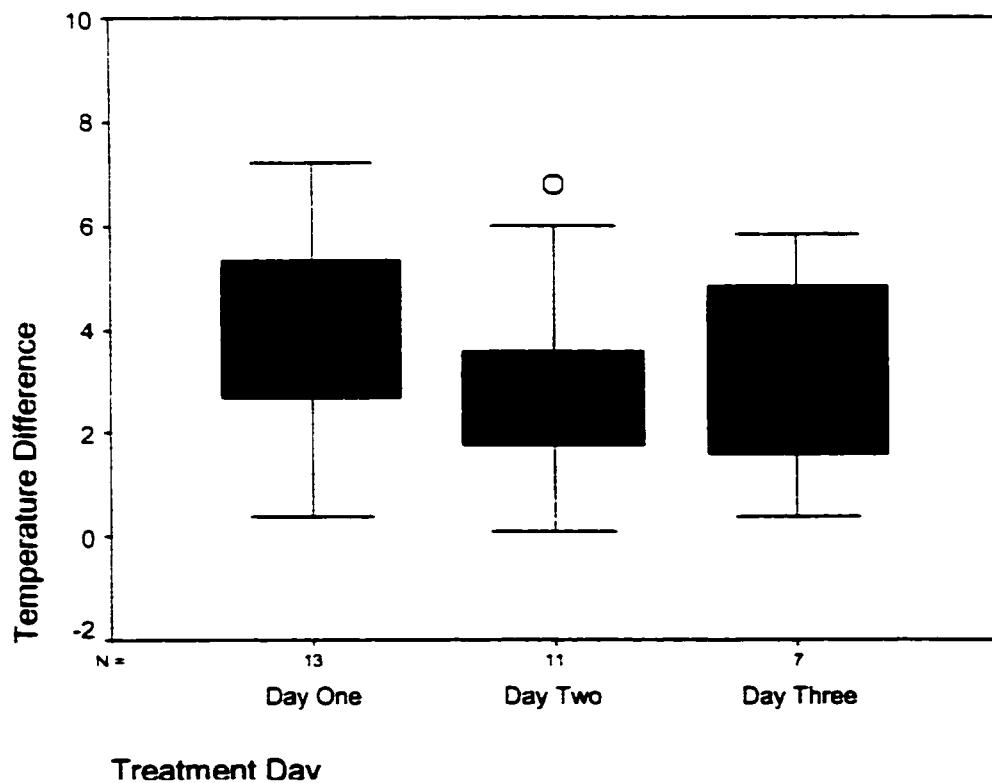
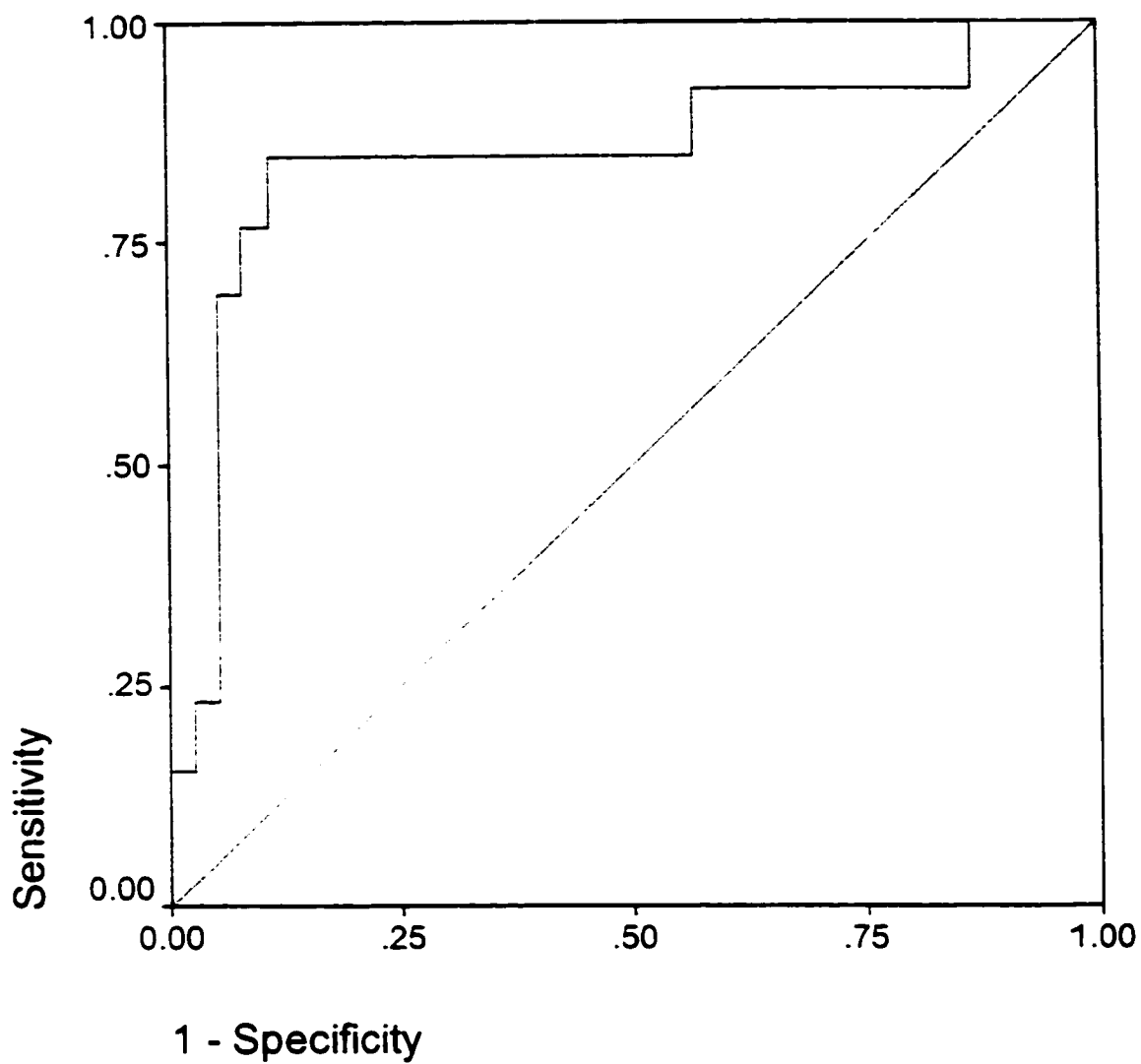
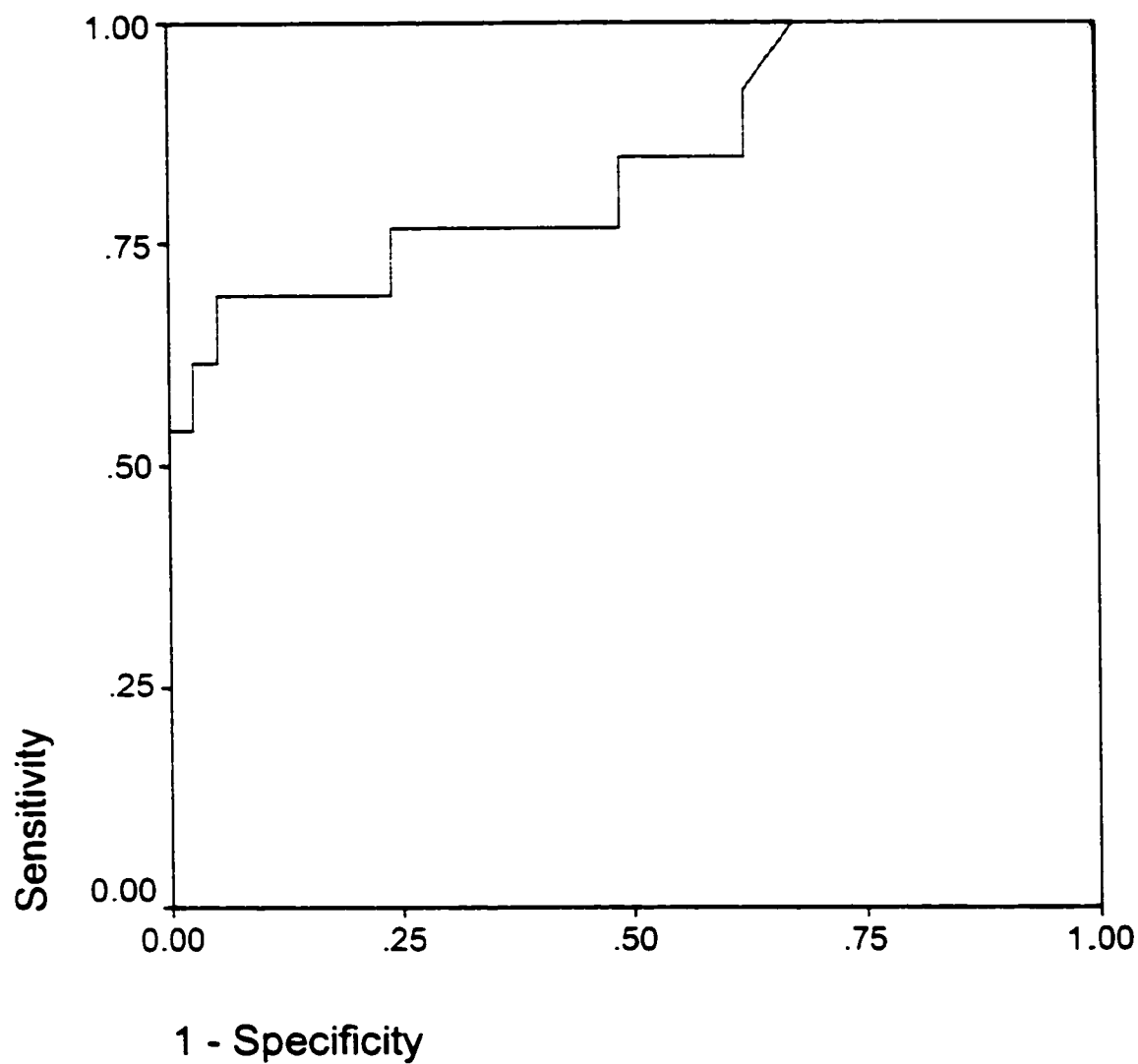


Figure 5: Receiver Operating Characteristic Curve Examining the Ability of the Slope of Area Change to Discriminate Between Clinical Responders and Treatment Failures



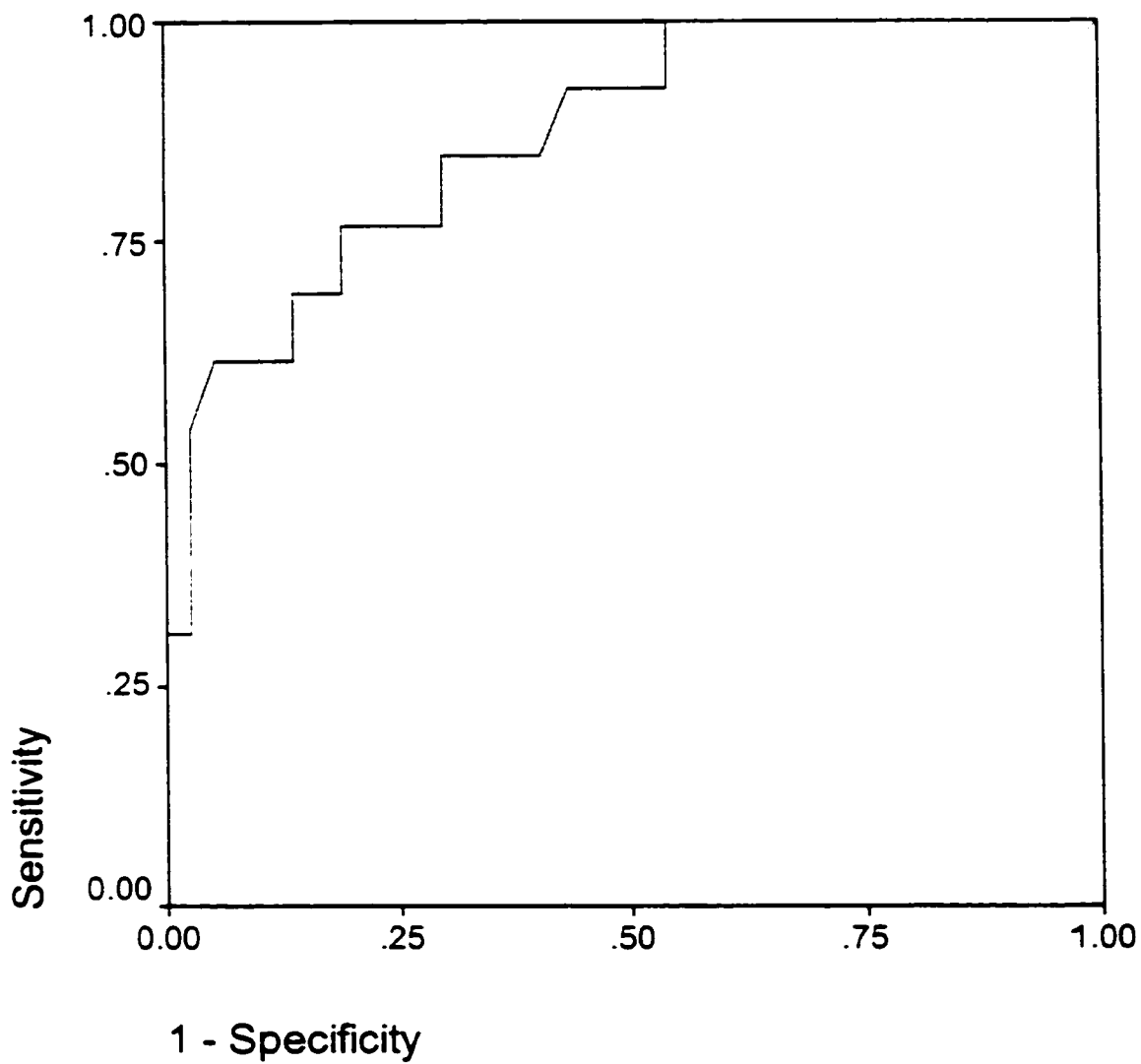
Area Under Curve With 95% Confidence Interval = 0.85 (0.70, 1.0)

Figure 6: Receiver Operating Curve Examining the Ability of the Slope of Change in Largest Diameter of Erythema to Discriminate Between Clinical Responders and Treatment Failures



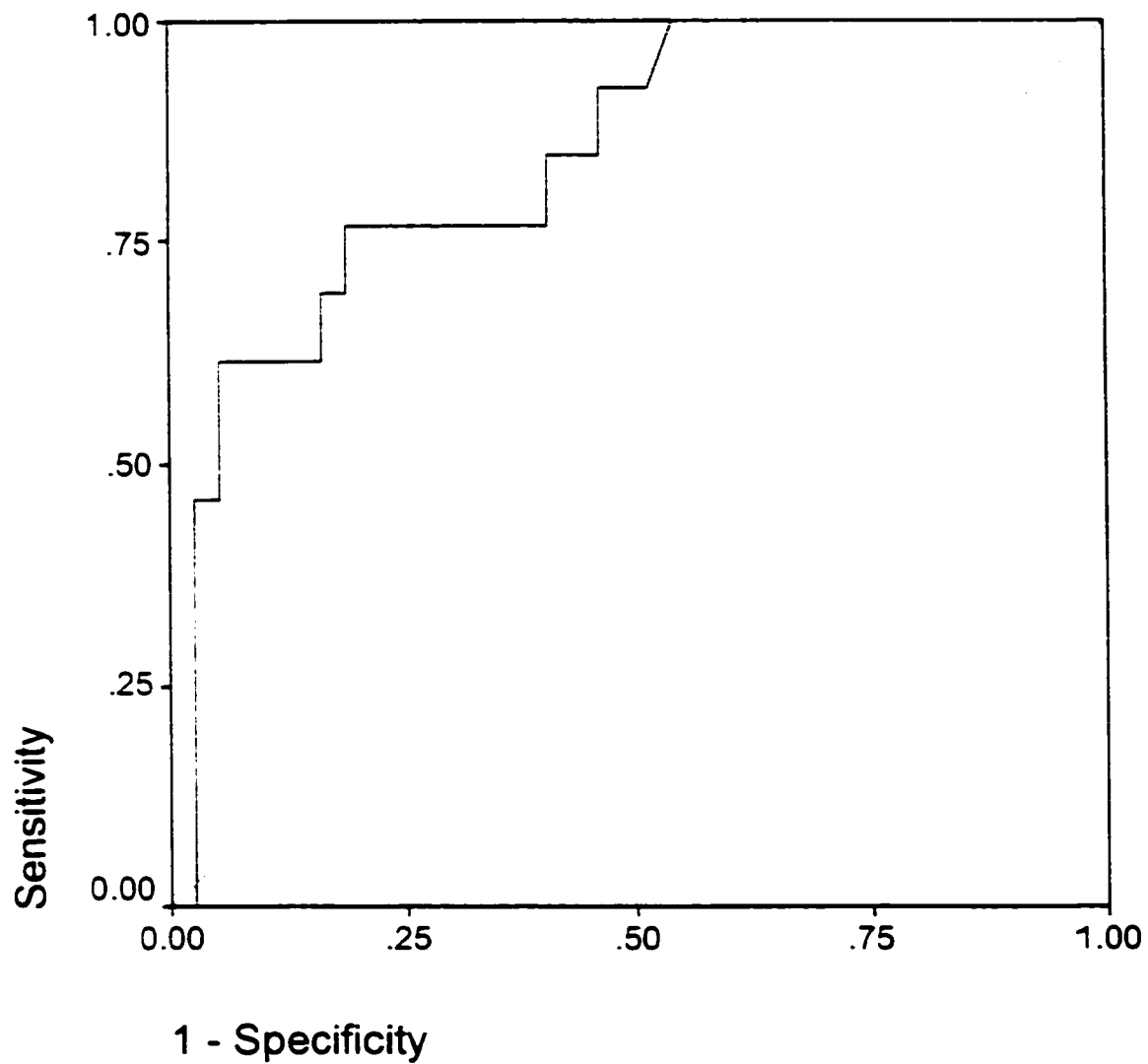
Area Under Curve With 95% Confidence Interval = 0.84 (0.70, 1.0)

Figure 7: Receiver Operating Curve Examining the Ability of the Ratio of Change in Area of Erythema to Discriminate Between Clinical Responders and Treatment Failures



Area Under Curve With 95% Confidence Interval = 0.87 (0.73, 1.0)

Figure 8: Receiver Operating Characteristic Curve Examining the Ability of the Ratio of Change in Erythema Diameter to Discriminate Between Clinical Responders and Treatment Failures



Area Under Curve With 95% Confidence Interval = 0.85 (0.73, 0.97)

Figure 9(a): Physician Impression of Infection Severity for 'Clinical Responders' During the First Three Days of Treatment Using a Five-Point Rating Scale (1 = Very Severe, 5 = Very Mild)

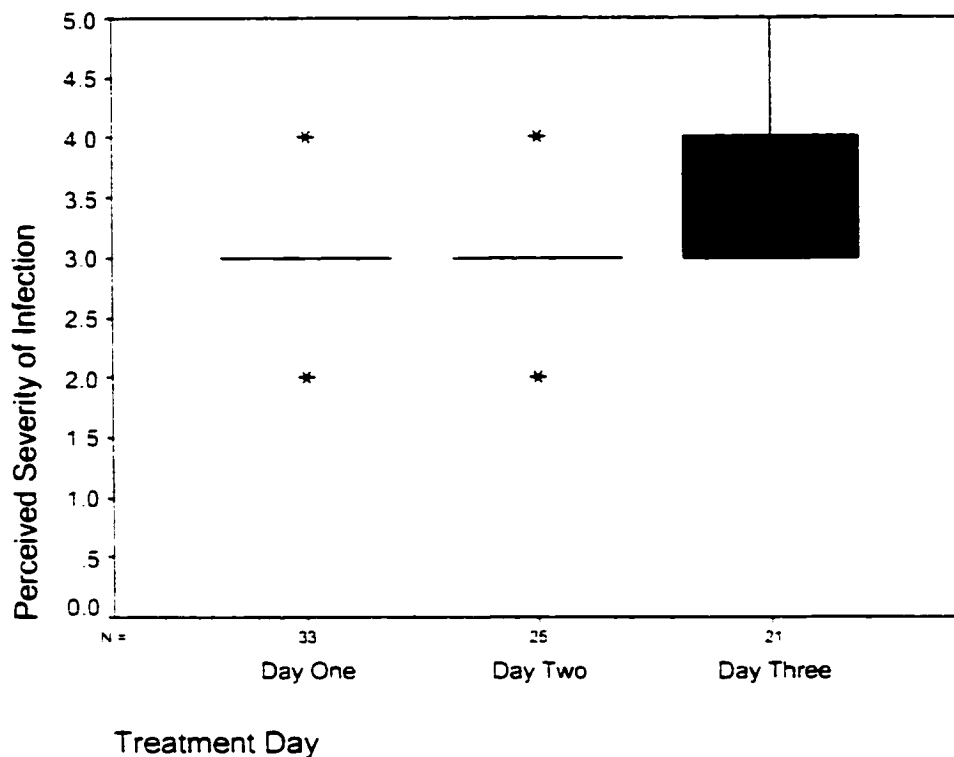


Figure 9(b): Physician Impression of Infection Severity for 'Treatment Failures' During the First Three Days of Treatment Using a Five-Point Rating Scale (1 = Very Severe, 5 = Very Mild)

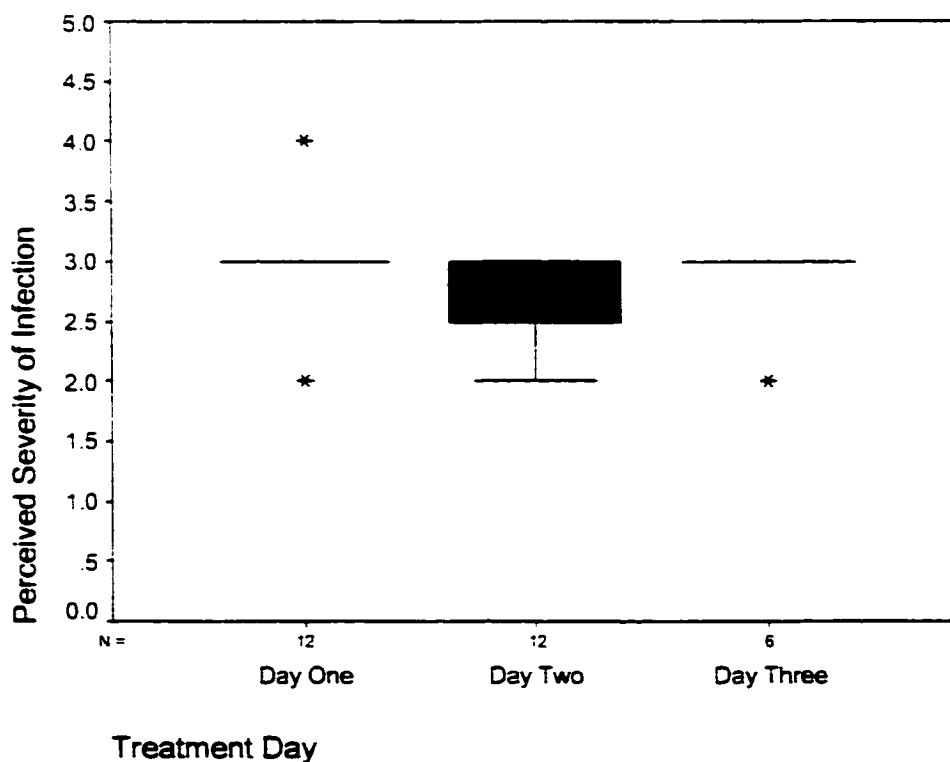


Figure 10(a): Patient Agreement With the Statement “My Infection is Better Than Yesterday” in the Clinical Responder Group During the First Three Days of Treatment

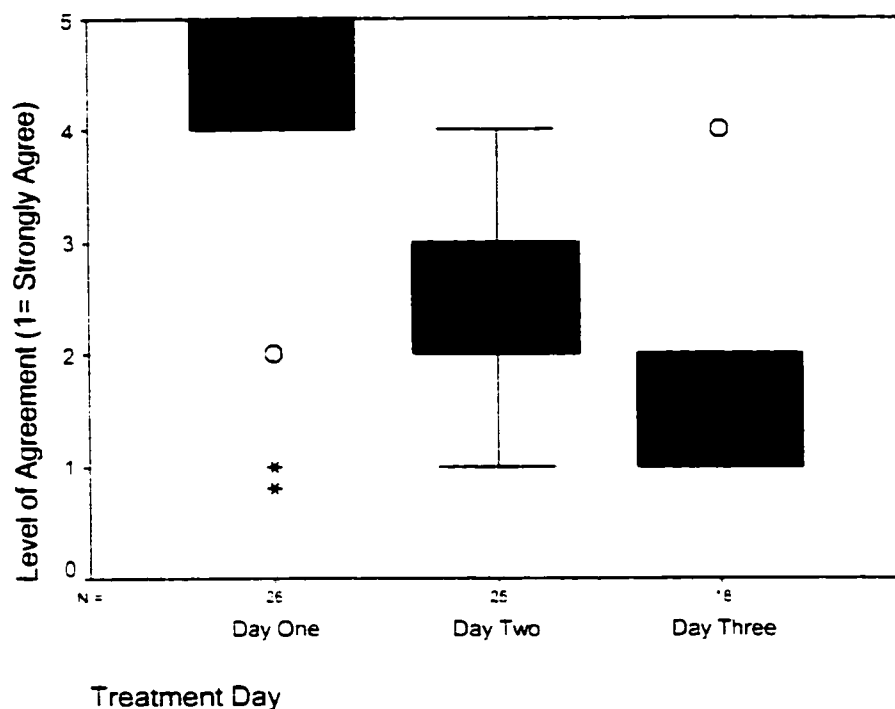


Figure 10(b): Patient Agreement With the Statement “My Infection is Better Than Yesterday” in the Treatment Failure Group During the First Three Days of Treatment

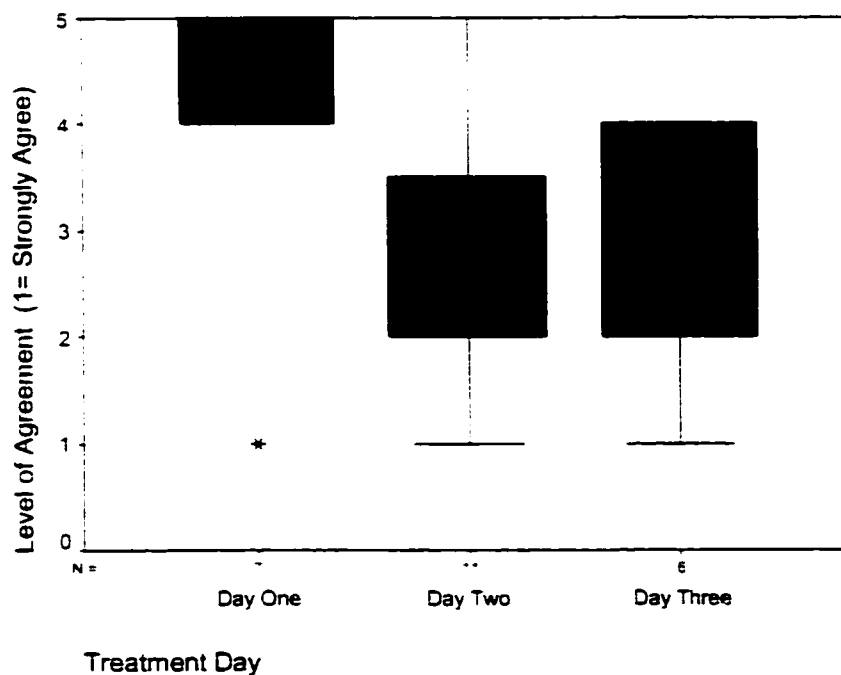
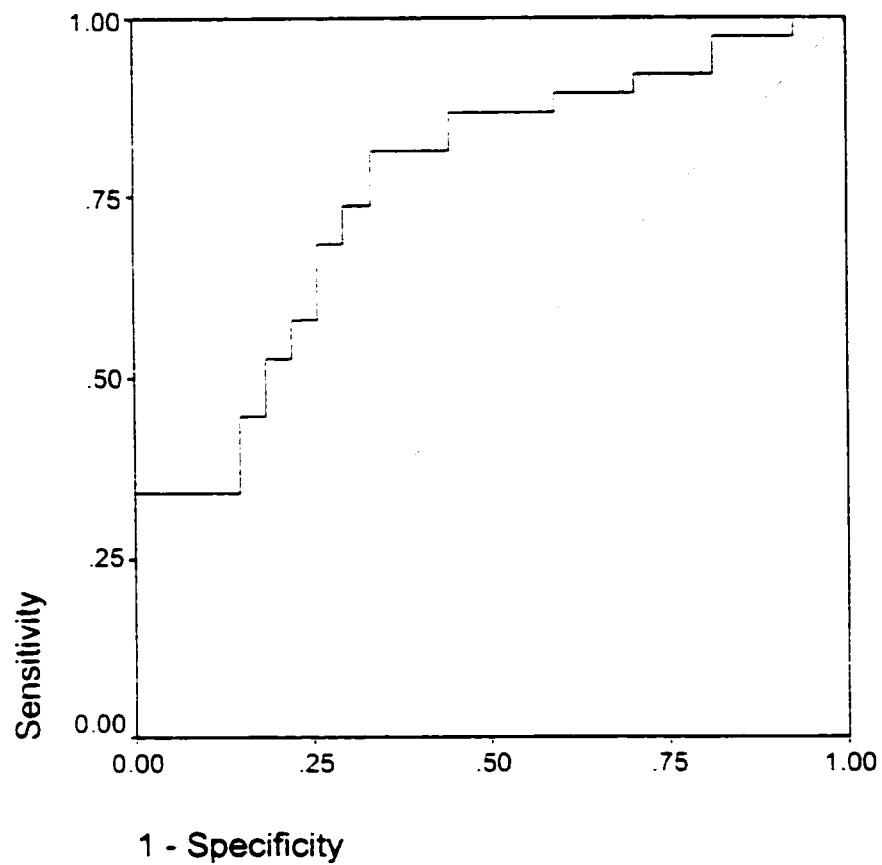
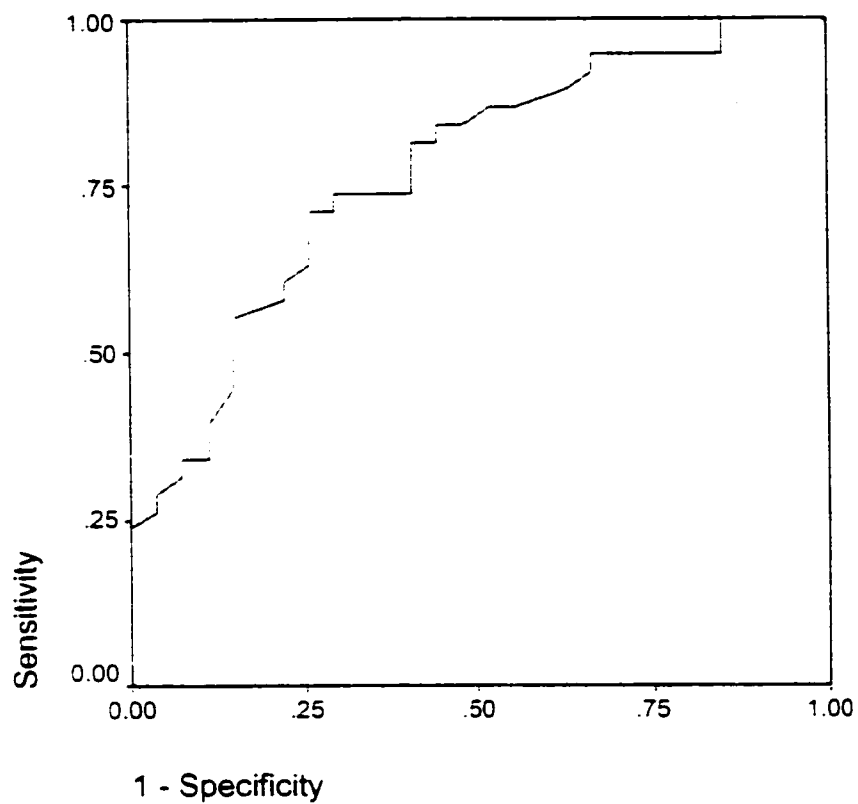


Figure 11: Receiver Operating Characteristic Curve for Initial Area of Erythema in Predicting Intravenous Antibiotic Treatment



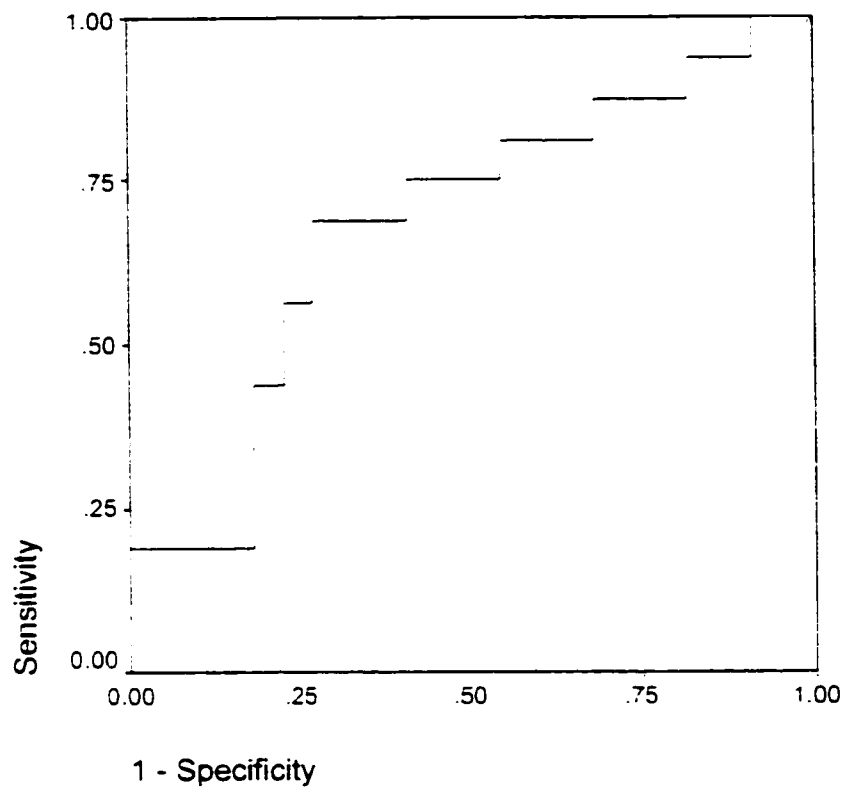
Area Under Curve (95% Confidence Interval): 0.78 (0.67, 0.90)

Figure 12: Receiver Operating Characteristic Curve for Initial Largest Diameter of Erythema in Predicting Intravenous Antibiotic Treatment



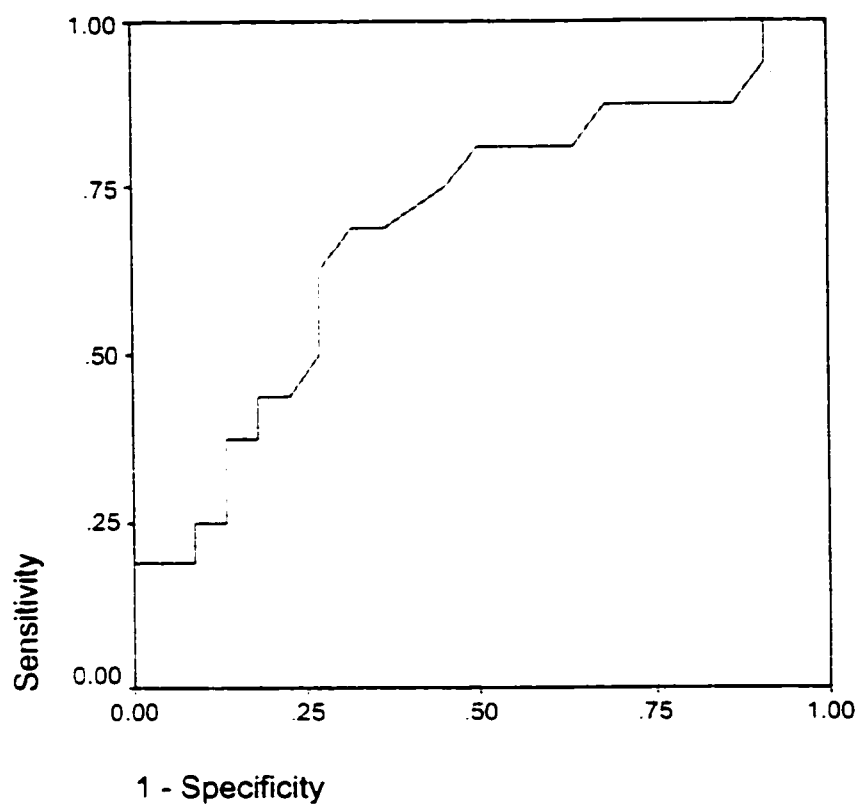
Area Under Curve (95% Confidence Interval): 0.76 (0.64, 0.89)

Figure 13: Receiver Operating Characteristic Curve Examining the Ability of the Largest Diameter of Erythema to Predict Intravenous Antibiotic Therapy (Once Other Significant Predictor Variables Have Been Removed)



Area under curve (95% Confidence Interval) 0.70 (0.47, 0.92)
N=28

Figure 14: Receiver Operating Characteristic Curve Examining the Ability of the Area of Erythema to Predict Intravenous Antibiotic Therapy (Once Other Significant Predictor Variables Have Been Removed)



Area under curve (95% Confidence Interval) = 0.69 (0.47, 0.92)
N=28

Appendix A

Queen's University Ethics Approval Form

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD REVIEW APPROVAL



Queen's University, in accordance with the "Tri-Council Policy Statement, 1998" prepared by the Medical Research Council, Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council of Canada requires that research projects involving human subjects be reviewed annually to determine their acceptability on ethical grounds.

A Research Ethics Board composed of:

Dr. A.F. Clark	Head and Professor, Department of Biochemistry, Professor, Department of Pathology, Faculty of Health Sciences, Queen's University (Chair)
Dr. B. Appleby	Departmental Assistant, Bioethics, Kingston General Hospital Instructor, Department of Family Medicine, Queen's University
Dr. M. Godwin	Associate Professor, Department of Family Medicine, Queen's University Associate Professor, Department of Community Health & Epidemiology Research Director, Department of Family Medicine, Queen's University
Dr. S. Irving	Psychologist, St. Mary's of the Lake Hospital
Ms. S. Laschinger	Assistant Professor, School of Nursing, Queen's University
Dr. J. Low	Professor, Department of Obstetrics and Gynaecology, Queen's University and Kingston General Hospital
Ms. F. O'Heare	Director, Risk Management Services, Kingston General Hospital Assistant Professor (Adjunct) School of Nursing, Queen's University
Dr. J. Parlow	Associate Professor, Department of Anaesthesia Assistant Professor, Department of Pharmacology & Toxicology, Queen's University
Dr. W. Racz	Professor, Department of Pharmacology & Toxicology, Queen's University
Dr. J. Rapin	Assistant Professor, Department of Emergency Medicine, Queen's University
Dr. M. Schumaker	Professor, Department of Religious Studies, Queen's University
Dr. L. Seymour	Co-Director, IND Program, NCIC Clinical Trials Group Associate Professor, Department of Oncology, Queen's University
Dr. S.J. Taylor	Bioethicist, Faculty of Health Sciences, Queen's University and Kingston General Hospital; Assistant Professor, Department of Family Medicine, Queen's University
Dr. G. Torrible	Community Member

has examined the protocol and consent form for the project entitled "Cellulitis in the ER: Developing and Testing Objective Outcome Measures" as proposed by Dr. Heather Murray of the Department of Emergency Medicine at Queen's University and considers it to be ethically acceptable. This approval is valid for one year. If there are any amendments or changes to the protocol affecting the subjects in this study, it is the responsibility of the principal investigator to notify the Research Ethics Board. Any adverse events must be reported to the Chair within 48 hours.

Albert F. Clark
Chair, Research Ethics Board

July 28, 1999
Date

ORIGINAL TO INVESTIGATOR - COPY TO DEPARTMENT HEAD - COPY TO HOSPITALS - P&T - FILE COPY

EMED-016-99
99-06-14

Appendix B

Cellulitis Study - MD Data Form

Patient Name / CR#

(attach ID sticker)

Date:

Draw a line around the erythema with a surgical marker pen. (first visit only)

Measurements:

- | | | | |
|----|--|-------|--------------------|
| 1) | Fever $>38^{\circ}\text{C}$ (reported by patient <i>or</i> documented in ER) | 0 Yes | 0 No |
| 2) | Other systemic symptoms (ie. nausea, vomiting, myalgias) | 0 Yes | 0 No |
| 3) | Lymphangitis or local lymphadenopathy | 0 Yes | 0 No |
| 4) | (a) Temperature (centre of infected skin): | _____ | $^{\circ}\text{C}$ |
| | (b) Temperature (skin on <i>opposite side</i> of body): | _____ | $^{\circ}\text{C}$ |
| 5) | (a) Largest diameter of erythema: | _____ | mm |
| | (b) Perpendicular diameter of erythema: | _____ | mm |
| 6) | Intensity of erythema (choose closest number on red scale): | _____ | |

Repeat Visits Only:

- | | | | | |
|----|---|-------|------|----|
| 7) | (a) Has erythema expanded beyond the original line? | 0 Yes | 0 No | |
| | yes: _____ mm | | | If |
| | (b) Has erythema shrunk inside the original line? | 0 Yes | 0 No | |
| | yes: _____ mm | | | If |

Physician Impression: *(circle most appropriate answer)*

- | | | | | | |
|-----|--|--------|----------|----------|-------------------|
| 8) | This patient has an abscess. | | | | |
| | Strongly agree | Agree | Unsure | Disagree | Strongly Disagree |
| 9) | Please attempt to classify the severity of this patient's infection: | | | | |
| | Very Severe | Severe | Moderate | Mild | Very Mild |
| 10) | Do you think that this patient would benefit from admission to hospital? | | | | 0 Yes 0 No |

Cellulitis Study - MD Data Form

Patient Impression:

10) My infection is better than yesterday. *(circle most appropriate answer)*

Strongly Agree Agree Unsure Disagree Strongly Disagree

11) Measure patient's pain. Please have the patient *place a mark along the 10 cm line* to indicate the pain they are experiencing from their infection.

0 _____ 10
(No pain) (Worst pain ever)

Cellulitis Study - Demographics / Outcome Form

Patient Name / CR#

(attach ID sticker)

Date:

History of Present Illness:

- 1) Location of infection: _____
- 2) Duration of Symptoms (*days*) : _____
- 3) Infection is **post-traumatic** (2° to laceration, abrasion or hematoma)
0 Yes 0 No
If "yes", describe trauma (including date): _____

- 4) Previous Antibiotic Treatment: 0 Yes 0 No
If Yes: _____ (name of antibiotic - route)
_____ (date Abx started / stopped)
2nd Abx (where applicable): _____ (name: route)
_____ (date started stopped)

Past Medical History:

- 1) Diabetes 0 Yes 0 No
Describe: _____
- 2) Peripheral Vascular Disease 0 Yes 0 No
Describe: _____
- 3) Peripheral Edema 0 Yes 0 No
- 4) Cardiovascular Disease 0 Yes 0 No
Describe: _____
- 5) Dermatologic Disorder 0 Yes 0 No
Describe: _____
- 6) Previous Cellulitis 0 Yes 0 No
Describe: _____

Cellulitis Study - Demographics / Outcome Form

Medications:

Allergies:

Date / Study day #:

Antibiotic Treatment:

(name/dose/route for previous 24hrs)

Incision and drainage attempted?	0 Yes	0 No
If Yes, date: _____		
Successful? (pus drained)	0 Yes	0 No
Specialist consulted?	0 Yes	0 No
If Yes, date: _____		
Specialty: _____		
Patient admitted?	0 Yes	0 No
Date admitted: _____		
Date discharged: _____		
Discharge Diagnosis: _____		

Appendix C

5 Point Ordinal Rating Scale for Intensity of Redness

