Non-Purulent Skin and Soft Tissue Infections in the Emergency Department

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Abstract

Non-purulent skin and soft tissue infections (SSTIs) involve the epidermis and dermis and are commonly managed in the emergency department (ED). Current guidelines lack evidence to guide clinicians on optimal management. The aim of this thesis was to describe the epidemiology of adults with non-purulent SSTIs presenting to the ED. Secondary goals were to identify factors associated with oral antibiotic treatment failure; describe an outpatient parenteral antibiotic therapy (OPAT) clinic-to-ED program; and determine physician rationale for selecting intravenous therapy. We conducted a health records review and prospective observational cohort study.

There was significant physician practice variation and an unexpectedly high hospitalization rate. We identified four factors associated with oral antibiotic treatment failure (tachypnea, chronic ulcers, history of methicillin resistant *Staphylococcus aureus* colonization or infection, and cellulitis in the past 12 months). An ED-to-OPAT clinic program was found to be safe, with low treatment failure rates and high patient satisfaction.

Executive Summary

Non-purulent skin and soft tissue infections (SSTIs) describe infections of the superficial epidermis and dermis (erysipelas) or involvement of the deep dermis and subcutaneous tissue (cellulitis). These infections are commonly diagnosed and managed in the emergency department (ED) setting. There are no studies that have described the epidemiology of adults with non-purulent SSTIs who are managed in the ED. Furthermore; current guidelines are based on expert opinion and lack evidence to guide physicians on the optimal route of antibiotic therapy (oral versus intravenous).

The aim of this thesis project was to describe the epidemiology of adults with non-purulent SSTIs who present to the ED. Secondary goals were to: (1) identify predictors associated with oral antibiotic treatment failure; (2) describe emergency physician rationale for selecting the intravenous route; and (3) describe the rate of treatment failure, adverse events and overall patient satisfaction for adults treated at an outpatient parenteral antimicrobial therapy (OPAT) clinic after initial diagnosis and management in the ED. To meet these goals, we conducted a health records review and prospective observational cohort study.

The findings from this thesis project are important first steps to better understand what factors predispose to oral antibiotic treatment failure, why emergency

physicians select the intravenous route, and patient outcomes in an ED-to-OPAT clinic model for management of non-purulent SSTIs.

Contributions of the Authors

Dr. Krishan Yadav is the first author of both manuscripts and was primarily responsible for study design, data collection, statistical analysis and writing of the manuscripts. Both manuscripts were co-authored by Dr. Yadav's thesis supervisors Dr. Ian G Stiell and Dr. George Wells, and thesis advisory committee member Dr. Kathryn Suh. Two medical students (Mr. John Macisaac and Mr. Darmyn Ritchie) aided in chart review and data collection for the health records review. Mr. Jordan Bernick provided helpful feedback regarding statistical analysis. Drs. Eagles and Thiruganasambandamoorthy provided helpful suggestions and feedback for both manuscripts. Drs. Stiell, Wells and Suh provided valuable feedback throughout the entire process.

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Abbreviations Used in the Text

SSTI – skin and soft tissue infections

ED – emergency department

OPAT – outpatient parenteral antibiotic therapy

CA-MRSA – community acquired methicillin resistant *staphylococcus aureus*

MRSA – methicillin resistant *staphylococcus aureus*

ABSSI – acute bacterial skin and skin structure infections

IDSA – Infectious Disease Society of America

CREST – clinical resource efficiency support team

PICC – peripherally inserted central catheter

CCAC – community care access centre

LHIN – local health integration network

CDER – center for drug evaluation and research

CI – confidence interval

OR – odds ratio

ICD-10-CA – International Classification of Diseases, 10th revision, Canada

IQR – interquartile range

Chapter One: Introduction

1. Introduction

Skin and soft tissue infections (SSTIs) refer to a spectrum of disease processes that encompass bacterial infections of the epidermis and deeper dermal layers. Severity ranges from superficial processes (erysipelas and cellulitis) to life- or limb-threatening infections of deeper structures (necrotizing fasciitis). Non-purulent SSTIs are the subset of infections that do not contain pus (a collection of white blood cells, nonviable tissues and degraded cellular contents). Non-purulent SSTIs are common and account for approximately 14.5 million cases annually in the United States alone.[1] However, clinicians are faced with many challenges in both diagnosis and management of this seemingly simple disease entity.

SSTIs remain a clinical diagnosis. There are many diagnostic mimics, including but not limited to: deep venous thrombosis; stasis dermatitis; hematoma; gout; and contact dermatitis. At times it may be difficult to differentiate non-purulent SSTIs from abscesses. This is important, as the latter is treated with surgical incision and drainage as opposed to antibiotics alone. There are no specific laboratory tests to confirm the diagnosis. The 2014 Infectious Disease Society of America guidelines in fact recommend against routine laboratory testing for non-purulent SSTIs – including blood tests, biopsy cultures or swabs.[2] Once the diagnosis is made, clinicians are expected to select appropriate antimicrobial therapy. Deciding on optimal treatment is complicated by the need to select not only the correct antimicrobial agent, but also the correct route of delivery (oral versus intravenous).

Due to the lack of evidence, current guidelines on management of SSTIs are based on expert opinion.[2,3]

2. Rationale

Accurate diagnosis and appropriate treatment of SSTIs are critical for patient safety, optimizing clinical outcome and decreasing healthcare costs and overall burden. The epidemiology of SSTIs has been well documented in two distinct populations: hospitalized patients and those who seek care at physicians' offices.[4-6] However, there are no studies that have described the epidemiology of adults with SSTIs who seek care in the Emergency Department (ED). This constitutes a significant evidence gap when one considers that SSTIs account for as much as 3% of all ED visits.[7] A thorough understanding of the epidemiology of non-purulent SSTIs in the ED patient population would provide an important basis toward developing more appropriate evidence-based recommendations for management of this common condition.

3. Thesis Goals and Objectives

The principal goal of this thesis is to obtain a thorough understanding of the epidemiology of non-purulent SSTIs in adults who are managed in a Canadian ED setting. A secondary goal will be to identify any variables independently associated with the outcome of treatment failure with oral and intravenous antibiotics at 14 days from the index ED visit. These goals will be addressed through a health records review (**Study A**) of all patients presenting to the ED with non-purulent SSTIs. A

third goal will be to describe the function and outcomes of an Outpatient Parenteral Antibiotic Therapy (OPAT) Clinic on adult ED patients with SSTIs that are felt to require intravenous therapy. This study will specifically describe the outcome of OPAT treatment failure and emergency physician rationale for selecting intravenous antibiotics for non-purulent SSTIs. A prospective observational cohort study of ED patients treated at the OPAT Clinic will be conducted (**Study B**) to address this final goal.

The objectives of each chapter in this thesis are as follows:

Chapter One
A brief introduction that provides: (a) the rationale and importance of researching ED patients with non-purulent SSTIs; (b) the thesis goals and objectives; and (c) the objectives of each chapter.

Chapter Two
This chapter provides the background discussion concerning the pathophysiology, diagnosis and outpatient management of non-purulent SSTIs in the ED setting.

Chapter Three
A manuscript of the health records review (**Study A**). The goals of the manuscript are to: 1) describe the epidemiology of non-purulent SSTIs in adults with SSTIs who present to the ED; and 2) identify variables independently associated with the

clinical outcome of treatment failure with oral antibiotics at 14 days from the index ED visit.

Chapter Four

A manuscript of the prospective observational cohort study (**Study B**). The goals of the manuscript are to: 1) describe outcomes of the OPAT Clinic in ED patients including OPAT treatment failure and patient adverse events; 2) assess patient satisfaction with OPAT; and 3) identify emergency physician rationale for selecting intravenous antibiotics.

Chapter Five

A discussion based on the combined results of **Study A** and **Study B**. In addition to summarizing the results and drawing conclusions, implications for future research will be determined.

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Chapter Two: Background

1. Introduction

Uncomplicated, non-purulent skin and soft tissue infections (SSTIs) describe infections of the superficial epidermis and dermis (erysipelas) or additional deeper involvement including the deep dermis and subcutaneous tissue (cellulitis).[1] Patients with non-purulent SSTIs present with redness, pain and swelling of the involved skin. It is important to note that there is an absence of any purulent (i.e. pus-containing) material or abscess. The Emergency Department (ED) physician must first establish the diagnosis, and then decide on the optimal agent, dose, frequency, route and setting for antimicrobial therapy. These decisions have been complicated further by the increasing prevalence of community acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA).[2,3] Appropriate diagnosis and management of SSTIs is crucial in order to prevent complications such as bacteremia or the development of necrotizing fasciitis.

2. Background

2.1 Classification

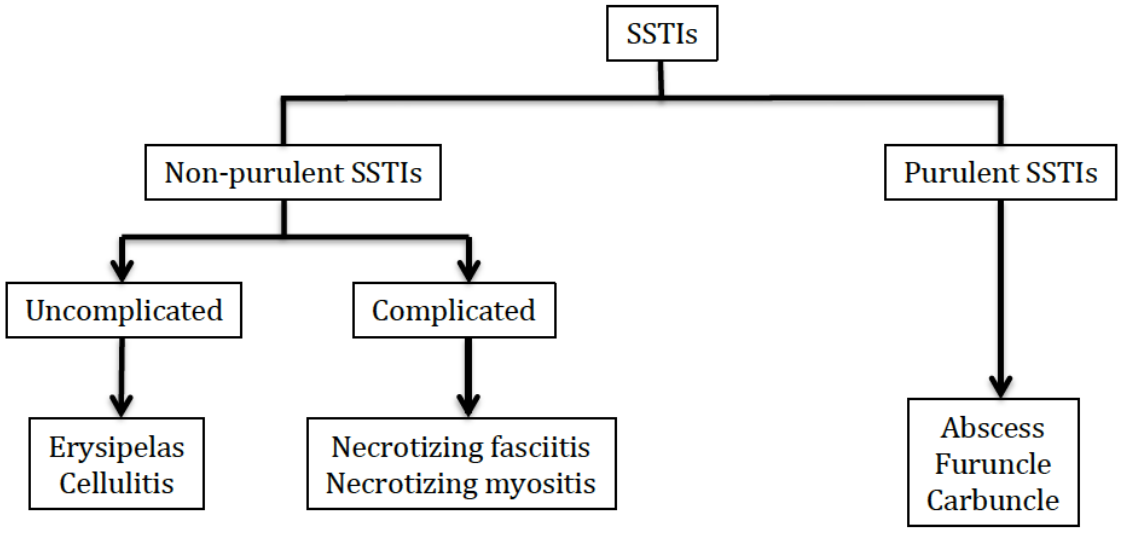
SSTIs may be subdivided into purulent or non-purulent categories (**Figure 1**). Purulent SSTIs are infections that contain pus, which is a collection of white blood cells, nonviable tissue and degraded cellular contents. Purulent SSTIs include furuncles (purulent material from the hair follicle – also called a boil); carbuncles (collection of furuncles with communicating tracts); and abscesses (deeper walled-off collection of purulent material). When feasible this subgroup is treated with

surgical incision and drainage. Antibiotics are recommended only if there are signs of systemic illness.[4] Non-purulent SSTIs are not amenable to surgical drainage. Instead, this subgroup is treated with antibiotics. Non-purulent SSTIs may be further subdivided into uncomplicated versus complicated categories. Uncomplicated non-purulent SSTIs include cellulitis and erysipelas. Complicated non-purulent SSTIs consist of life-threatening necrotizing infections of deeper tissues, including the fascia or muscle. Necrotizing infections are rapidly progressive and create significant destruction of tissue. Patients with necrotizing infections classically present with severe pain out of proportion to the findings on clinical exam, and are at risk of limb loss or even death. The focus of this thesis is on the most common subset: uncomplicated, non-purulent SSTIs.

2.2 Incidence & Burden of Disease

SSTIs are a common condition diagnosed and managed in EDs and carry significant financial burden on healthcare systems globally. From 1997 to 2005, the number of Americans seeking medical care for SSTIs increased by 50%, with 14.2 million visits in 2005 alone.[5] Patients with SSTIs account for up to 3% of all ED visits in the United States, translating to 3.4 million visits.[6,7] Although Canadian data are lacking, a single Vancouver ED diagnosed 2234 patients with a SSTI between January 2003 and September 2004, representing 2% of all ED visits.[8] A 2011 report by the Canadian Institute for Health Information found that cellulitis was the 5th and 7th most common reason for an ED visit in the 45 to 64 and greater than 65 years age groups, respectively.[9]

Figure 1. Classification of skin and soft tissue infections (SSTIs)



SSTIs are responsible for a significant healthcare system burden due to hospital admission and subsequent costs. SSTIs managed in the ED result in a 13.9 – 15.2% hospital admission rate, with the most common cited reason being the need for intravenous antibiotics.[10,11] Hospitalization for complicated SSTIs, termed acute bacterial skin and skin structure infections[12], result in an average cost of $8023 with a mean hospital length of stay of 4.9 days.[13] One study found that from 2005 to 2011, the rate of admission for ABSSI increased by 17%, accounting for 2% of all hospital admissions in the United States.[14]

2.3 Etiology & Risk Factors

Group A streptococcus (*Streptococcus pyogenes*), β-hemolytic group B, C and G streptococci, and *Staphylococcus aureus* are the most common offending bacteria. Typically, a portal of entry that disrupts the protective cutaneous barrier

predisposes a patient to developing an SSTI. Examples include skin trauma, surgical incisions, injection drug use, and ulcer formation. Additional risk factors for non-purulent SSTIs include: lymphedema, venous insufficiency, obesity, prior history of cellulitis and tinea pedis. Of note, case-control studies failed to find any association observed with diabetes mellitus, alcohol or smoking.[15,16] In a minority of cases, the source of infection may be hematogenous seeding or idiopathic.

2.4 Clinical Features & Complications

Patients typically present with pain, redness, swelling and induration of the affected skin. Patients with cellulitis have irregular, patchy borders of affected reddened skin. Conversely, the borders are well demarcated, raised and palpable in patients with erysipelas. In some cases, there may be lymphangitis (erythematous streaking along the affected extremity along the distribution of the blood vessels) or lymphadenopathy (painful swelling of lymph nodes). A minority of patients may also exhibit systemic signs such as fever or tachycardia. If treated with appropriate antimicrobial therapy, uncomplicated non-purulent SSTIs should resolve within five to seven days. Patients may experience mild pain and redness for several days beyond this timeframe as the residual inflammation subsides.

Some patients may suffer complications such as sepsis or bloodstream infections (bacteremia) that warrant hospital admission. On occasion, apparent non-purulent infections develop into walled-off abscesses that require surgical incision and drainage. If not promptly treated, cellulitis involving a preexisting ulcer may

progress to infect underlying bone (osteomyelitis), which often requires several weeks of antimicrobial therapy. Serious adverse events such as limb amputation or death are rare.

2.5 Diagnosis

Wound cultures are not possible for non-purulent SSTIs. A systematic review found the rate of bacteremia secondary to cellulitis or erysipelas ranged from less than 1% to 7.9%.[17] Blood cultures are typically low yield and rarely change management. Thus, adjunct tests are unhelpful and the diagnosis of SSTIs remains a clinical one.

However, diagnosis of uncomplicated non-purulent SSTIs remains challenging. A recent large cross-sectional study found a 30.5% misdiagnosis rate of lower extremity cellulitis (termed '*pseudocellulitis*'). The study authors estimated this misdiagnosis rate would result in 50,000 to 130,000 unnecessary hospitalizations and $195 to $515 million US dollars in excess healthcare spending.[18] The difficulty in the accurate diagnosis of SSTIs is due to several mimics, such as: stasis dermatitis; lymphedema; gout; deep vein thrombosis; and cutaneous drug eruption.

2.6 Current Guidelines

Owing to a lack of high quality evidence, empiric treatment guidelines based on expert opinion have been published to aid clinicians.[4,19-21] There are currently no Canadian guidelines for the management of SSTIs. Despite the increasing burden of this common presentation, current evidence is lacking regarding the optimal

management of SSTIs. A recent Cochrane review concluded that the optimal antimicrobial therapy for SSTIs remains unclear, as no two randomized controlled trials, among the 25 identified studies, compared the same two antibiotic regimens.[21] Recent studies have shown promise for novel once-weekly parenteral lipoglycopeptide antibiotics for the treatment of SSTIs, which may be especially useful in communities that lack the resources to implement outpatient parenteral antibiotic therapy (OPAT). These have the potential to decrease the healthcare system burden, lower complication rates from repeat intravenous doses, and provide added convenience for patients.[22,23]

Practice guidelines published by the Infectious Disease Society of America (IDSA) are based on expert consensus, again highlighting the lack of published data to determine an optimal management strategy.[4] In the United Kingdom, the Eron classification system was developed by an expert panel and has been incorporated into the Clinical Resource Efficiency Support Team (CREST) guidelines.[19,24] An alternative Dundee classification was developed based on retrospective data, and has been shown to reduce the number of patients treated by parenteral antibiotics by 70% in comparison to the Eron classification.[25,26] However, the Dundee classification scheme has not been incorporated into any consensus guidelines.

It has been postulated that only a sparse inoculum of bacterial pathogen causes SSTIs, and that the associated significant inflammatory response is responsible for the physical findings of pain, redness and induration that patients experience.[27]

Based on this rationale, Hepburn and colleagues reported that a shorter 5-day course of antibiotics was equally efficacious as a longer 10-day course.[28] Current guidelines recommend that uncomplicated non-purulent SSTIs should be treated with anti-streptococcal antibiotics for a duration of 5 days.[4]

2.7 Oral versus Intravenous Therapy

Selecting the optimal route of antimicrobial therapy is a key decision point in the management of SSTIs for emergency physicians. Oral antibiotic therapy holds several advantages over the parenteral route, including lower risk of complications, decreased cost, and increased patient convenience and comfort.[29,30] Oral therapy is generally preferred, in particular for infections in otherwise well appearing immunocompetent hosts without signs of systemic illness, such as fever and vomiting.

Patients who receive intravenous lines are at risk of both local and systemic intravenous catheter-related infections, such as bacteremia. There is also a risk of thrombophlebitis – a painful inflammation of the vein due to a thrombus. Intravenous formulations are more costly than their oral counterparts. There is also the additional cost of medical supplies (intravenous lines, tubing, needles, etc.) and trained healthcare personnel to administer the medication. In areas where an OPAT service is not available, there is also a significant cost incurred due to hospital admission. Intravenous therapy carries the added inconvenience of a lack of

mobility for patients and a risk of having to return to the ED due to complications such as a blocked or dislodged peripheral intravenous line.

The only absolute indications for intravenous therapy are: 1) an inability to swallow pills or absorb the medication from the gastrointestinal tract; and 2) the oral medication achieves poor concentrations in the circulation (poor bioavailability). The former indication is uncommon in the ED for patients with SSTIs. Furthermore, most oral antibiotics used to treat SSTIs have good to excellent bioavailability.[30,31] There are currently no studies that have examined why emergency physicians select intravenous antibiotic therapy.

Only two studies have compared oral versus intravenous therapy within the same antibiotic class for the treatment of SSTIs. Jorup and colleagues conducted a small quasi-randomized trial comparing oral versus intravenous penicillin for erysipelas, and found no benefit with intravenous therapy.[32] The outcomes assessed in this study were fever duration, hospital length of stay, and sick leave. A more recent small randomized trial by Aboltins and colleagues found oral cephalexin was non-inferior to intravenous cefazolin for the primary outcome of days until no advancement in the area of cellulitis.[33] Unfortunately, neither trial was powered to detect a difference in treatment failure, which is an outcome that is more clinically important and impactful. To date, there are no published studies that have demonstrated a benefit of intravenous antibiotics over oral therapy for the management of non-purulent SSTIs. It stands to reason that if SSTIs can be

adequately treated with oral therapy, then this is clearly more preferable, given the increased cost and risks associated with intravenous therapy.

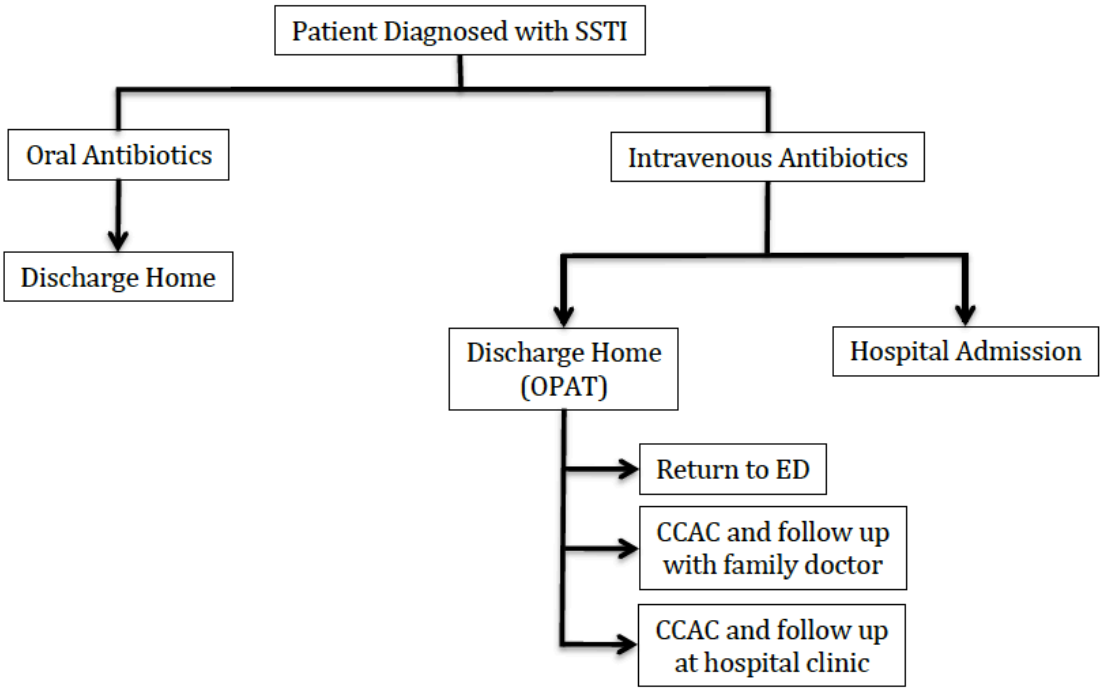
2.8 ED Treatment

Several treatment pathways exist for ED patients diagnosed with SSTIs (**Figure 2**). The emergency physician must decide on the most appropriate route of antibiotic therapy. The majority of patients are treated as outpatients with oral antibiotics. If patients are either systemically ill or are felt to have failed oral therapy, then the intravenous route is selected. For patients in which intravenous therapy is chosen, patients are either admitted to hospital or may receive their treatment in the community, which is also referred to as outpatient parenteral antibiotic therapy (OPAT).

2.8.1 Oral Antibiotic Therapy

The majority of patients diagnosed with non-purulent SSTIs in the ED are treated as outpatients with oral antibiotics. Current guidelines recommend a 5-day course of oral antibiotic therapy.[4] Despite this, surveyed Canadian emergency physicians indicated that they more commonly prescribe a 7 or 10-day course of oral antibiotics.[34] Patients are typically asked to follow up with their family physician in 48 to 72 hours for a reassessment, but are instructed to return to the ED if symptoms worsen (spreading erythema or signs of systemic illness). Some emergency physicians mark the borders of erythema with a pen, to help patients determine if the erythema is spreading well outside of its initial borders.

Figure 2. ED Treatment Pathways for Patients with SSTIs



SSTI = skin and soft tissue infection; ED = emergency department; OPAT = outpatient parenteral antibiotic therapy; CCAC = Community Care Access Centre

2.8.2 Parenteral (Intravenous) Antibiotic Therapy

Intravenous antibiotics are chosen if patients are systemically ill, have a severe clinical presentation based on the physician's impression, or are unable to tolerate oral therapy. These patients are either treated in the hospital or discharged home to receive OPAT (**Figure 2**).

2.8.2.1 Inpatient Parenteral Antibiotic Therapy

Inpatient care may be warranted for several reasons. First, there may be concerns about a patient's ability to be compliant with outpatient therapy. This may include social issues such as homelessness, an inability to travel, psychiatric illness, and injection drug use. Second, the clinician may decide that the infection is severe enough to require closer observation and management as an inpatient. Third, the patient may already have complications such as sepsis and/or unstable vital signs (e.g. hypotension, tachycardia). Fourth, a minority of patients may be worsening clinically, despite already receiving intravenous antibiotics in the community, and are deemed to have failed OPAT.

2.8.2.2 Outpatient Parenteral Antibiotic Therapy (OPAT)

There are three methods of intravenous antibiotic delivery using the OPAT model: 1) in the ED; 2) via a trained nurse or self-administration in the patient's home; or 3) via a trained nurse at an ambulatory clinic. First reported in 1974, OPAT is generally defined as the administration of at least two doses of parenteral antimicrobials on different days without interim hospitalization.[35] OPAT is most commonly used to treat SSTIs, but may also be utilized for a variety of other infections, including: urinary tract infections, osteomyelitis, central nervous system infections and endocarditis.[36,37] The following discussion about OPAT is in reference to SSTIs only.

Appropriate patient selection is critical to the success of an OPAT program. Following diagnosis, the emergency physician must decide that the patient requires

parenteral rather than oral antibiotic therapy. There are currently no published data regarding how emergency physicians decide that parenteral therapy is required for patients with SSTIs. Moreover, there are no evidence-based guidelines to help clinicians decide on when the parenteral route is appropriate. In addition to the infection itself, several other factors may play a role in physician decision-making, such as: comorbidities, triage vital signs and signs of systemic illness. Social factors must also be considered. For example, homeless patients or those without a means of travel may be poor candidates for OPAT. Many OPAT programs exclude intravenous drug users due to safety concerns, and only one small observational study suggests OPAT in this patient population may be safe and effective.[38] Finally, use of OPAT must be acceptable to the patient and caregivers.

Following patient selection, the emergency physician must select the optimal antimicrobial agent. Antibiotics with long half-lives, such as ceftriaxone, may be attractive choices due to less frequent dosing that would be more convenient for patients. However, unnecessarily broad-spectrum antibiotics carry the risk of selecting for antimicrobial resistance due to alterations in the gut flora with subsequent overgrowth of resistant bacteria. When surveyed, 76.5% of Canadian emergency physicians preferred cefazolin as the first choice parenteral antibiotic for SSTIs.[34] Vancomycin or other antimicrobials with activity against CA-MRSA should be considered in patients with a purulent SSTI and risk factors, such as hepatitis C or substance abuse.[39]

Patients are usually discharged with a peripheral intravenous catheter in place for further antimicrobial doses. A peripherally inserted central catheter (PICC), which is a more permanent intravenous catheter that can generally remain in place for the duration of treatment, may be placed at a later date if it is determined that prolonged therapy is required. The final step is to determine the appropriate follow-up for patients receiving OPAT. Depending on locally available resources, patients can receive follow-up with emergency physician in the ED, with a family practitioner, or in a hospital clinic setting with an infectious disease specialist.

2.8.2.2.1 Return to the ED

In communities that do not have resources to administer intravenous antibiotics outside of the hospital, patients are asked to return to the ED for subsequent doses. An emergency physician usually performs a clinical reassessment within 24 to 72 hours to determine if the infection is responding to therapy. Patients with a good response are stepped down to oral therapy, whereas those with little response but no signs of systemic illness and no worsening may be continued with intravenous therapy. These patients would be scheduled for another ED reassessment at a later date. Patients whose infections are clinically worsening despite parenteral therapy are admitted to hospital.

This approach is clearly cumbersome for patients, particularly for those who do not have an appropriate means to travel to and from a clinic or hospital. Furthermore, reassessment at a later date is rarely with the same emergency physician, which

makes it difficult to provide an objective clinical assessment regarding response to therapy. Another approach involves the use of ED observation units to monitor patients with SSTIs in the ED for up to 24 hours before making a final decision to admit to hospital or manage as an outpatient, resulting in high admission rates ranging from 29.2 to 38%.[40,41] It is generally accepted that SSTIs take at least 48 to 72 hours before improvement may be noted. It is therefore unlikely that a short stay in an observation unit would impact the decision to admit or discharge a patient and would instead add to ED crowding.

2.8.2.2.2 Community Care Access Centre (CCAC) & Family Physician Follow-Up

In Ontario, Canada, the provision of healthcare in the community or at home is managed by Local Health Integration Networks (LHINs). The LHIN of a specific region oversees the Community Care Access Centre (CCAC), which provides nursing services for wound care and administration of parenteral antibiotics. A pharmacist is also involved in medication review. In Ontario, CCAC services are an integral part of the OPAT model. Most patients visit a clinic to receive intravenous doses by a trained nurse. A smaller subset of patients (usually older patients who cannot travel) receives intravenous doses within their own home. In communities with CCAC services but without timely access to infectious disease specialists, patients are advised to seek a clinical reassessment from their family physician.

2.8.2.2.3 CCAC & Return to a Hospital Clinic

Many urban hospitals have set up clinics run by infectious disease specialists to follow and manage patients being treated in the community with intravenous antibiotics. For example, patients at The Ottawa Hospital who are treated with OPAT receive follow-up and reassessment with an infectious disease specialist at the OPAT Clinic. This model provides several theoretical advantages: 1) decreased hospital admissions; 2) increased patient convenience; and 3) decreased ED visits for antimicrobial therapy and reassessments. While this intuitively appears to be the ideal approach, no published data currently exist regarding the efficacy of OPAT in the community setting.[42]

2.8.2.2.4 OPAT Adverse Outcomes

Administration of OPAT for SSTIs is not without risk. There is the potential of progression of infection despite OPAT, line-related complications or adverse drug reactions that may warrant subsequent hospital admission. Petrak *et al.*[43] recommended that studies about the efficacy of OPAT should incorporate robust definitions for treatment failure.

The reported hospital admission rate following OPAT treatment failure ranges from 2.6% to 8%.[43-45] However, these studies examined a variety of infectious diseases, making it difficult to determine the clinical failure rate for SSTIs in particular. A retrospective study reported a readmission rate of 5.5% for cellulitis, although the reasons for hospitalization were not described.[46] There is a lack of studies concerning non-purulent SSTIs using robust definitions for OPAT treatment failure.

2.9 Questions Surrounding Optimal ED Management of SSTIs

Before determining the optimal outpatient management strategy for ED patients with SSTIs, there are three key questions that arise:

1) What is the definition of (i) *oral antibiotic treatment failure* and (ii) *OPAT treatment failure*?
2) Are there predictors of treatment failure with oral antibiotics? In other words, which patients require parenteral therapy?
3) When considering the optimal route of therapy, what is the ED physician's rationale when selecting parenteral therapy?

2.10 Treatment Failure

2.10.1 Treatment Failure as an Outcome in the ED Setting

In 2013, the US Center for Drug Evaluation and Research (CDER) released guidelines to help researchers standardize future clinical trials for SSTIs. The CDER defines clinical response as a reduction in lesion size greater or equal to 20% compared to baseline, evaluated 48 to 72 hours after therapy is initiated.[12] Based on this definition of treatment 'improvement', one can infer that treatment failure would then be defined as a reduction in lesion size less than 20% at 48 to 72 hours.

This definition of treatment failure is problematic in the ED setting. First, the majority of ED physicians will only see patients with SSTIs during a single encounter. Second, many patients are prescribed oral antibiotics for SSTIs in the

clinic setting and then present to the ED. The emergency physician is left with the dilemma of whether their current presentation truly reflects a treatment failure. The emergency physician also often does not have any objective data (photographs or medical records) to reasonably estimate the lesion size and severity when oral antibiotics were initiated.

A number of studies in the ED setting have reported treatment failure as an outcome. Murray and colleagues defined treatment failure as any of the following: specialist consultation, hospital admission, surgical procedure (e.g. incision and drainage), an 'upgrade' from oral to parenteral therapy, or a change in class of intravenous antibiotics due to lack of clinical response.[47] This definition was based on expert opinion and the authors' own observation of treatment patterns in their Emergency Department. A 2011 ED study of pediatric patients that defined treatment failure used a similar definition, once again based on expert opinion.[48] Peterson and coworkers defined treatment failure as subsequent hospitalization, a change in class of antibiotic, or a switch from oral to parenteral therapy.[49] Patients requiring subsequent incision and drainage were excluded from this definition.

Of note, the authors reporting treatment failure as an outcome in the aforementioned studies did not specify a timeframe at which clinical assessment for treatment failure should be undertaken. This is clinically important as assessing a patient too soon after the initiation of antibiotic therapy may result in an inappropriate diagnosis of treatment failure. Additionally, it is notable that these ED

studies did not incorporate a change in lesion size into their definitions of treatment failure, as this is impractical in the ED setting. A recent systematic review identified 19 randomized controlled trials with reported treatment failure rates for cellulitis ranging from 6 to 37%.[50] The authors speculated that this high degree of variability might be due to difficulty with diagnosis and confusion with cellulitis mimics. In addition, variability in treatment failure rates is likely also related to the lack of a uniform definition for treatment failure.

2.10.2 Treatment Failure Definition

There is currently no validated definition of treatment failure following antibiotic therapy for SSTIs. Due to the unique nature of the patient population and care delivered in the ED, it is important to use a definition tailored to this setting. Using a specific percentage in reduction of lesion size is impractical for the following reasons: 1) physicians may not document dimensions of the infection; 2) many ED (electronic medical) records do not allow for photographs to be uploaded; and 3) patients may be already on oral antibiotic therapy initiated by a family physician and do not present with documentation of lesion size at onset of therapy. Instead, it is more pragmatic to use clinical judgment when determining treatment failure. It would be appropriate to conclude a treatment failure has occurred if the patient reports significant spread of infection, there are systemic signs of illness (e.g. fever, tachycardia) or if the clinician feels the infection is severe despite an appropriate duration of therapy.

The United States Food and Drug Administration recommends that clinical response to treatment should be assessed at 48 to 72 hours from initiating therapy.[51] When surveyed, a majority of Canadian emergency physicians selected 48 hours as the optimal timeframe for determining if treatment failure had occurred following initiation of antibiotic therapy.[34] After review of the literature[40,47-49,52-54] and discussion with local experts in emergency medicine and infectious disease, the following two definitions of treatment failure for non-purulent SSTIs were developed:

A. Oral Antibiotic Treatment Failure

Oral antibiotic treatment failure is defined as any of the following outcomes that occurs within 14 days of the initial ED visit and after a minimum of 48 hours of oral antibiotic therapy: (i) subsequent hospital admission for an SSTI; (ii) a change in class of oral antibiotic owing to progression of infection and not due to intolerance or allergy; or (iii) a change in antibiotic route from oral to intravenous therapy.

B. OPAT Treatment Failure

OPAT treatment failure is defined as subsequent hospital admission after a minimum of 48 hours of OPAT for any of the following: (i) infection progression; (ii) line-related complications (e.g. bacteremia, thrombophlebitis, venous thromboembolism); or (iii) drug-related complications (e.g. *Clostridium difficile* colitis).

Adverse events such as operative debridement, amputation or death were felt to be unhelpful components of the aforementioned definitions because they are rare.

2.11 Predictors of Treatment Failure With Oral Antibiotics

Identifying predictors of failure with oral antibiotics is important for two reasons. First, having knowledge of predictors with oral therapy would help emergency physicians identify the subset of patients that should be started on intravenous therapy at the initial visit, limiting the overuse of parenteral therapy and subsequently reducing the associated adverse events and costs. Second, the risk of sepsis and subsequent hospital admissions may be reduced in patients inappropriately started on oral therapy. There are currently no ED studies reporting risk factors for failure with oral antibiotics. An understanding of these risk factors would be critical toward developing evidence-based criteria for patients that require intravenous therapy.

A systematic review of SSTIs managed in the ED observation unit reported that fever, leukocytosis and known MRSA exposure were the most commonly reported risk factors for treatment failure.[55] Peterson and coworkers identified five risk factors independently associated with treatment failure for cellulitis: fever, chronic leg ulcers, chronic edema or lymphedema, prior cellulitis in the same area, and cellulitis at a wound site.[49] However, these studies did not discriminate between failures with oral versus intravenous therapy.

2.12 Oral Versus The Intravenous Route: Emergency Physician Rationale for Selecting Intravenous Therapy

The ideal antimicrobial agent in the treatment of non-purulent SSTIs would possess the following characteristics: (i) optimal pharmacokinetic properties against the causative organism; (ii) minimal adverse effects; (iii) inexpensive; and (iv) acceptable to patients and healthcare providers. Oral antibiotics are preferred to intravenous antibiotics in that they pose fewer risks of adverse events, are cheaper, and are less invasive to patients. The main point of contention lies in the ability of the antimicrobial agent to achieve adequate concentrations in blood and tissue, for an adequate duration to arrest bacterial growth. Therefore, an oral agent would be clearly preferable if it can achieve high tissue and serum concentrations that are comparable to their parenteral counterparts. For example, oral cephalexin achieves excellent (90 to 100%) bioavailability[31] and is an excellent choice to treat non-purulent SSTIs.

Yet ED-based studies have shown that intravenous antibiotics are more commonly administered[47,49] and that antibiotic overuse is common.[56] May and coworkers reported that while 87% of surveyed attending emergency physicians felt that antibiotics were overused in the ED, only 10% believed they themselves overprescribed antibiotics.[57] One plausible explanation is that patients presenting to the ED may have more severe infections. Other possible explanations include a perception that parenteral therapy is superior, a consideration of significant comorbidities, or concerns about compliance with oral medications.

Surprisingly, there is scant literature addressing emergency physician decision-making regarding antibiotic prescribing[57], and there are no published studies describing physician rationale for selecting intravenous antibiotics for infections. Identifying the factors physicians consider when opting for parenteral therapy would be highly useful for carrying out clinical trials to test these perceived indications.

3. Rationale

Patients commonly seek ED care for non-purulent SSTIs, which require extensive healthcare resources for both inpatient (hospital resources) and outpatient (CCAC; physician follow up) management. Identifying predictors of treatment failure with oral antibiotics would allow emergency physicians to more appropriately select patients that require intravenous therapy. This may also help reduce the number of patients inappropriately treated with more costly parenteral therapy that carries the added risk of adverse events. Furthermore, determining the reasons behind selecting parenteral therapy is a critical first step in understanding emergency physician decision-making for the management of SSTIs. Finally, despite being the most common indication for OPAT, treatment failure in the OPAT setting has not been described for SSTIs in particular. Thus, it is important to describe the overall performance and safety of OPAT therapy for SSTIs in the Canadian setting.

Accurate diagnosis and appropriate treatment of SSTIs are critical for patient safety and decreasing healthcare costs and overall burden. The epidemiology of SSTIs has

been well documented in two distinct populations: hospitalized patients and those who visit physicians' offices.[58-60] However, there are no studies that have described the epidemiology of adults with SSTIs who are seen and managed in the ED setting. As a majority of ED adult patients are treated as outpatients, this constitutes a significant evidence gap. A thorough understanding of the epidemiology of non-purulent SSTIs seen in the ED is an important basis for developing more appropriate evidence-based recommendations for optimal management of this common condition.

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Chapter Three: Predictors of Oral Antibiotic Failure for Non-Purulent Skin and Soft Tissue Infections in the Emergency Department

Chapter Overview

The following is a manuscript prepared for publication based on a health records review. The objectives of this health records review were: 1) to describe the epidemiology of adult patients with non-purulent skin and soft tissue infections who present to the emergency department; and 2) to identify risk factors associated with oral antibiotic treatment failure.

In **Appendix A** a copy of the approval letter from the Ottawa Health Science Network Research Ethics Board is provided.

In **Appendix B** a detailed description is provided of the methods used to develop a multivariable logistic regression model for predictors of oral antibiotic treatment failure.

Dr. Krishan Yadav is the first author of this manuscript and was responsible for the study development, data collection, monitoring of data abstraction, statistical analysis and writing of the manuscript. This manuscript was co-authored by Dr. Ian Stiell, Dr. Kathryn Suh and Dr. George Wells. Jordan Bernick provided valuable input regarding data analysis. Dr. Debra Eagles and Dr. Venkatesh Thiruganasambandamoorthy provided valuable feedback throughout the process. Mr. John Macisaac and Mr. Darmyn Ritchie were involved with data abstraction.

Predictors of Oral Antibiotic Failure for Non-Purulent Skin and Soft Tissue Infections in the Emergency Department

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Abstract

Introduction

Current guideline recommendations for optimal management of non-purulent skin and soft tissue infections (SSTIs) are based on expert consensus, rather than on evidence. There is currently a lack of evidence to guide emergency physicians on when to select oral versus intravenous antibiotic therapy.

Methods

We performed a health records review of adults (age ≥18 years) with non-purulent SSTIs treated at two tertiary care emergency departments (EDs). Patients were excluded if they had a purulent infection or infected ulcers without surrounding cellulitis. Multivariable logistic regression was used to identify predictors independently associated with oral antibiotic treatment failure after a minimum of 48 hours of oral therapy.

Results

We enrolled 500 patients (mean age 64 years, 279 male (55.8%) and 126 (25.2%) with diabetes). The hospital admission rate was 29.6%. Of 288 patients who had received a minimum of 48 hours of oral antibiotics, there were 85 oral antibiotic treatment failures (29.5%). Tachypnea at triage (odds ratio [OR] = 6.31; 95% CI 1.80, 22.08), chronic ulcers (OR = 4.90; 95% CI 1.68, 14.27), history of MRSA colonization or infection (OR = 4.83, 95%; CI 1.51, 15.44), and cellulitis in the past

12 months (OR = 2.23, 95% CI = 1.01, 4.96) were independently associated with oral antibiotic treatment failure.

Conclusion

This is the first study to evaluate potential predictors of oral antibiotic treatment failure for non-purulent SSTIs in the ED. We observed a high hospital admission rate and practice variability regarding antimicrobial agent and route. Tachypnea at triage, chronic ulcers, history of MRSA colonization or infection and cellulitis within the past year were independently associated with oral antibiotic treatment failure. Emergency physicians should consider these risk factors when deciding on oral versus intravenous antimicrobial therapy for non-purulent SSTIs being managed as outpatients.

Introduction

Uncomplicated, non-purulent skin and soft tissue infections (SSTIs) describe bacterial infections of the superficial epidermis and dermis (erysipelas) or deeper dermis and subcutaneous tissue (cellulitis) in which patients experience redness, pain and induration of the involved skin. Non-purulent and purulent SSTIs are a common clinical problem, accounting for up to 3% of all emergency department (ED) visits in the United States, translating to 3.4 million visits.[1,2] Although Canadian data are lacking, a single Vancouver ED diagnosed 2234 patients with a SSTI, representing 2% of all ED visits.[3] Once the diagnosis of a non-purulent SSTI is made, the emergency physician must select the appropriate antibiotic agent, dose, duration and route (oral or intravenous).

Due to a lack of high quality evidence, empiric treatment guidelines are based on expert opinion.[4-6] Selecting the appropriate antibiotic route for outpatient management is a key decision point. Oral therapy holds several advantages over the parenteral route, including: lower risk of complications, decreased cost, increased patient convenience and comfort.[7-9] Intravenous therapy may be selected if a patient has failed oral therapy, is systemically unwell or has a severe infection based on the clinician's impression. The main advantage of the intravenous route is optimizing bioavailability, which is especially useful in patients with swallowing difficulty or a gastrointestinal malabsorption syndrome. The intravenous route is costlier, less convenient for patients and has an added risk of adverse events. There are currently no studies that have aimed to identify predictors associated with treatment failure

with oral antibiotic therapy. Identification of such predictors would allow emergency physicians to better select patients that require intravenous antibiotics. This may also help reduce the number of patients inappropriately treated with parenteral therapy.

The primary objective of this study was to identify risk factors associated with oral antibiotic treatment failure for non-purulent SSTIs. A secondary objective was to describe the epidemiology of adults with non-purulent SSTIs presenting to the ED.

Methods

Study Design and Setting

We performed a health records review of consecutive adult patients presenting to the ED with diagnosis and management of a non-purulent SSTI. The study population was enrolled from the Ottawa Hospital Civic and General EDs, both being tertiary care adult EDs with a combined 170,000 patient visits annually. The Ottawa Health Science Network Research Ethics Board approved the protocol without the need for informed consent.

Population

We enrolled a consecutive sample of patients meeting eligibility criteria that presented to the ED over a seven-month period (January 1 to July 31, 2016). Eligible patients were adults (age ≥ 18 years) presenting to the ED and diagnosed with a non-purulent SSTI that was treated with either oral or intravenous antibiotics. Patients were considered eligible if they were already taking antibiotics at the index ED visit. We excluded patients for the following reasons: (i) patients presenting for a

follow-up visit (i.e. not the index ED visit for this clinical problem); (ii) age < 18 years; (iii) a diagnosis of a purulent skin abscess where an incision and drainage procedure was performed; (iv) infected ulcers without surrounding cellulitis or erysipelas; or (v) necrotizing infections.

Study Protocol and Data Abstraction

In order to minimize bias, we took specific steps with respect to case selection, abstractor training, definition of variables, use of a standardized case record form, regular meetings and oversight of abstractors in accordance with accepted methodology for chart reviews.[10-13] We identified eligible cases by International Classification of Diseases, 10th revision, Canada (ICD-10-CA) diagnosis codes of L03* (cellulitis, unspecified) and A46 (erysipelas). Relevant patient data were obtained from the electronic health record (physician and nursing notes, outpatient parenteral antibiotic therapy (OPAT) clinic records).

The principal investigator (KY) trained two medical students (JM, DR) on the use of the electronic health records system. All variables and the primary outcome of interest were explicitly defined (see supplementary appendix) a priori. We used a standardized case record form (see supplementary appendix) to abstract data. The case record form was piloted to remove ambiguous items and ensure the data collection instrument was robust. The data abstractors held regular monthly meetings to resolve any disagreements by consensus. The principal investigator monitored the performance of the data abstractors by reviewing 25% of the sample.

Cohen's kappa statistic was used to assess interobserver agreement for included subjects and the primary outcome.

Outcome Measures

The primary outcome was treatment failure with oral antibiotics. There is currently no validated definition of treatment failure in the literature. The United States Food and Drug Administration recommends that clinical response to treatment should be assessed at 48 to 72 hours from initiating therapy.[14] When surveyed, a majority of Canadian emergency physicians selected 48 hours as the optimal timeframe for determining if treatment failure had occurred following initiation of antibiotic therapy.[15] After review of the literature[16-22] and discussion with local experts in emergency medicine and infectious disease, we devised a treatment failure definition. Treatment failure with oral antibiotics was defined as any of the following outcomes occurring after a minimum of 48 hours of oral antibiotics and at no later than 14 days from the index ED visit: (i) subsequent hospital admission for a SSTI; (ii) a change in class of oral antibiotic owing to progression of infection and not due to intolerance or allergy; or (iii) a change in antibiotic route from oral to intravenous therapy owing to progression of infection and not due to intolerance or allergy.

A secondary outcome of interest was treatment failure with intravenous antibiotics. This was defined as any of the following outcomes after a minimum of 48 hours of intravenous antibiotics and at no later than 14 days from the index ED visit: (i)

subsequent hospital admission for a SSTI; or (ii) a change in class of intravenous antibiotic owing to progression of infection and not due to intolerance or allergy.

The following baseline demographics and clinical data were abstracted: patient age and gender; comorbidities; ED triage vital signs; and infection characteristics. We anticipated that accurate infection dimensions (length and width) might not be consistently recorded on patient charts. In order to estimate the percent body surface area of affected skin, the modified Lund-Browder chart was used. [23,24] ED treatment variables were abstracted as follows: antibiotic treatment approach; and setting for subsequent intravenous antibiotics (if chosen). Adverse outcomes included antibiotic events and intravenous catheter-related events.

Statistical Analysis

The prevalence of non-purulent SSTIs in the ED population, the proportion of patients who received oral versus intravenous therapy, and the patients who had a treatment failure were calculated. Continuous data are presented as means with standard deviations or medians with an interquartile range (IQR, Q1 – Q3) for normally and non-normally distributed data, respectively. Categorical data are presented as proportions with 95% confidence intervals.

We employed univariate analyses to examine all clinical variables hypothesized to be risk factors for treatment failure with oral antibiotic therapy (see supplementary appendix). Variables with p-values of 0.10 or less were considered for multivariable analysis. A backwards selection procedure was used to obtain a multivariable

logistic regression model to determine clinical predictors independently associated with the primary outcome of treatment failure with oral antibiotics. The Hosmer-Lemeshow statistic was used to assess model fit. SAS (version 9.4, SAS Institute, Cary NC) was used for descriptive statistics, univariate and multivariable logistic regression analysis.

Sample Size and Feasibility

Previous studies have suggested that a minimum of 10 events per variable is required to avoid biased estimates when developing multivariable prediction models.[25-27] We estimated that no more than five predictor variables would be included in a model to predict treatment failure with oral antibiotics. Based on the 10 events per variable working rule, a minimum of 50 treatment failures would be required to develop a robust model. Treatment failure rates reported in the literature range from 6 to 37%.[28] Previously published studies in Canadian EDs have indicated that the approximate treatment failure rate of SSTIs with antibiotics ranges from 18.7 to 20.5%.[16,17] Assuming a conservative estimate of an 18% treatment failure rate, 270 patients would be required to obtain a minimum of 50 oral antibiotic treatment failures. We estimated that up to 40% of patients might be treated with intravenous therapy. Therefore, we determined an overall sample size of 500 patients would ensure that we surpassed the minimum required number of patients treated with oral antibiotics. From January 1, 2014 until December 31, 2014, there were 2286 unique visits to either the Civic or General campus of The Ottawa Hospital with an ICD-10 diagnosis of cellulitis or erysipelas. Even after

accounting for purulent SSTIs, a health records review of patients with non-purulent SSTIs over seven months would yield well over the minimum required sample size.

Results

Over the seven-month study period, 666 cases were screened for eligibility and 500 patients met the inclusion criteria (Figure 1). The kappa statistic for included cases between the primary investigator (KY) and each abstractor (JM and DR) was 0.96 (95% CI 0.93, 0.99) and 0.91 (95% CI 0.86, 0.97), respectively. The kappa statistic for the primary outcome of oral antibiotic treatment failure was 0.94 (95% CI 0.90, 0.98). Of the 500 enrolled patients, 126 (25.2%) had diabetes and 87 (17.4%) had a history of cellulitis in the prior 12 months (Table 1). The most common location of infection was the leg (54.2%) and most infections (80.2%) were estimated to be <5% total body surface area (Table 2).

Of the total cohort, 354 patients (70.8%) received an intravenous antibiotic in the ED, with 148 patients (29.6%) admitted to hospital for further parenteral therapy. The most common oral agent used was cephalexin and the most common parenteral agent was cefazolin (Table 3). Of patients receiving intravenous antibiotics, 20.6% received two or more antibiotics.

Of the 352 patients that were managed as outpatients, the majority (61.4%) received solely oral antibiotic prescriptions (Table 4). A significant proportion of

outpatients (19.9%) received an intravenous antibiotic dose in the ED but were discharged with an oral antibiotic prescription. Of the 222 patients receiving oral antibiotic prescriptions, cephalexin was most commonly selected (77.4%). Of the 136 patients who were prescribed outpatient intravenous antibiotics, 99 patients (72.8%) were referred to the OPAT clinic for assessment and follow up with an infectious disease specialist. A minority was asked to follow up with their primary care provider or return to the ED for follow up. Cefazolin (68.4%) was the most commonly prescribed intravenous antibiotic.

A significant number of outpatients (40.6%) returned to the ED within 14 days (Table 5). The majority of patients returned for scheduled repeat intravenous antibiotics, because of a delay in arranging intravenous antibiotics in the outpatient setting. A small proportion of unscheduled visits (5.4%) was for a worsening infection that required hospital admission. There were few adverse events for outpatients: 2.8% with a dislodged or blocked peripheral intravenous line; 1.7% of with gastrointestinal symptoms and 0.6% of with a rash attributed to the prescribed antibiotic.

For the 99 patients referred to the OPAT clinic, 85.8% of patients attended their appointment (Table 6). Emergency physicians diagnosed cellulitis with a high degree of accuracy (96.5%), with only three patients having an alternate diagnosis assigned by the infectious disease physicians. The median time to follow up for the

first OPAT clinic visit was 4 days and there was a median of 2 clinic visits. Patients received a median duration of 7 days of intravenous antibiotics.

Of 288 patients who were treated with at least 48 hours of oral antibiotics, 85 patients (29.5%) suffered an oral antibiotic treatment failure (Table 7). Treatment failures were managed as follows: 51 patients (60.0%) were switched to outpatient intravenous antibiotics; 30 patients (35.3%) were hospitalized for intravenous therapy; and 4 patients (4.7%) were switched to a different class of oral antibiotic. Of 212 patients treated with at least 48 hours of intravenous antibiotics, 12 patients (5.7%) suffered an intravenous antibiotic treatment failure (see the supplementary appendix).

Predictors associated with oral antibiotic treatment failure using multivariable logistic regression are shown in Table 8. Tachypnea at triage (odds ratio [OR] = 6.31; 95% CI 1.80, 22.08), chronic ulcers (OR = 4.90; 95% CI 1.68, 14.27), history of MRSA colonization or infection (OR = 4.83; 95% CI 1.51, 15.44), and cellulitis in the past 12 months (OR = 2.23; 95% CI 1.01, 4.96) were found to be independently associated with oral antibiotic treatment failure. The Hosmer-Lemeshow chi-square test yielded a p-value of 0.604 (χ^2 = 1.853, degrees of freedom = 3) and the C-statistic was 0.709. This indicates that our model has good fit.

Discussion

Interpretation of Results

This study describes adult patients presenting to the ED for non-purulent SSTIs. A substantial proportion of patients was admitted to hospital for further management. We observed significant practice variation with respect to selection of antimicrobial route and agent. A number of patients received a single intravenous dose in the ED followed by outpatient oral therapy, despite a lack of evidence to support this approach. The variability in treatment approach reinforces the lack of agreement amongst emergency physicians on the optimal approach to therapy for this common clinical condition.

We found an oral antibiotic treatment failure rate of 29.5%, which was higher than expected. Murray et al.[16] reported an oral antibiotic treatment failure rate of 6.8%, but this was a small sample size (2 of 29 patients). Peterson et al.[17] reported an oral antibiotic treatment failure rate of 21.0%. As neither study used a strict time cutoff in their definition of treatment failure, some patients may have been classified as an oral antibiotic treatment failure prematurely. We identified potential risk factors for failure with oral antibiotics. Tachypnea at triage, chronic ulcers, history of MRSA colonization or infection and cellulitis within the past year were independently associated with oral antibiotic treatment failure. These risk factors may be considered as potential indications for intravenous therapy. The high treatment failure and hospital admission rates are of concern. These findings may in part reflect the lack of evidence to guide emergency physicians on the optimal route of antimicrobial therapy.

Previous Studies

The most recent Infectious Disease Society of America guidelines suggest intravenous antibiotics for 'moderate' (signs of systemic illness) or 'severe' (failed oral therapy, signs of systemic illness, clinical signs of deeper infection, or immunocompromised) infections.[4] The British Clinical Resource Efficiency Support Team (CREST) guidelines recommend oral therapy in 'Class I' patients, defined as having no signs of systemic toxicity and no 'uncontrolled' comorbidities, which was not explicitly defined.[5] Due to a lack of evidence, these guidelines are based on expert opinion. A study by Peterson et al. identified predictors of failure with outpatient antibiotics for cellulitis, but did not distinguish between oral versus intravenous routes.[17] A recent survey of Canadian emergency physicians revealed that 94.4% of respondents would consider a clinical decision rule to predict oral antibiotic treatment failure.[15] To date, evidence regarding the optimal route of antimicrobial therapy for non-purulent SSTIs is lacking.

Strengths

This is the first study to identify potential predictors associated with oral antibiotic treatment failure for non-purulent SSTIs. There was excellent agreement between data abstractors for both inclusion of studies and the primary outcome. The study findings may better guide emergency physicians to determine when oral antibiotic treatment failure is likely – and when to select intravenous therapy at the onset of treatment.

Limitations

This health records review has several potential limitations. First, potentially clinically important variables (infection size and obesity) may have been inaccurate

or not documented. Obtaining accurate measures of infection size was not possible as it was seldom documented in the medical record. We instead attempted to estimate infection size using a Lund-Browder burn chart as a surrogate for total body surface area of affected skin. Obesity was not consistently documented in the medical chart and was not validated (e.g. by calculating the body mass index). We attempted to mitigate this by reviewing all electronic health records in the 6 months prior to and after the index visit to identify if this comorbidity was documented.

Second, the data abstractors were not blinded to the study outcome. This is unlikely to have resulted in significant bias as the primary outcome was strictly defined using a 48-hour cutoff for consideration of treatment failure. In addition, there was excellent inter-observer agreement for the primary outcome. We attempted to minimize bias by training abstractors, holding regular meetings, validating 25% of charts, defining variables a priori, and using a standardized case record form in accordance with accepted methodology for chart reviews.[10-13]

Third, there is no validated definition of oral antibiotic treatment failure. Following a review of the literature[14-22,29] we developed a composite endpoint definition after discussion and consensus among local experts in emergency medicine and infectious disease. Disadvantages of using a composite endpoint include misleading results if one component of the outcome heavily drives the result, especially if it is the least patient-important outcome. However, 95.3% of the treatment failures were

driven by the two most patient centred outcomes: hostpital admission for intravenous therapy or switch from oral to intravenous outpatient therapy.

Fourth, there was a small amount of missing data (<2.5%), which was assumed to be missing completely at random. We handled the missing data using a complete case analysis. Lastly, we were unable to measure adherence to treatment due to the nature of the study design.

Clinical Implications

Our findings reveal important clinical implications, having demonstrated significant practice variability with respect to selection of antimicrobial agent and route. Patients who received OPAT had a median duration of antibiotic therapy that was longer than the guideline-recommended five days.[4] Patients requiring intravenous therapy have more complicated infections, which may explain why they required a longer duration of therapy. This variation in treatment approach coupled with a high hospital admission rate is likely due to a lack of evidence-based recommendations for optimal therapy. Several risk factors associated with oral antibiotic treatment failure were identified. We believe that such factors should be considered when deciding on the optimal route of therapy. Ultimately, our findings highlight that further studies are critical to improve treatment of this common clinical condition.

Research Implications

Future research should involve a prospective study to further assess these potential risk factors for treatment failure identified in our study and ideally derive a clinical decision rule to guide emergency physicians on the optimal route of antimicrobial therapy. Furthermore, studies examining rationale for selecting intravenous therapy would provide better insight regarding physician decision-making.

Conclusions

This is the first study to evaluate potential predictors of oral antibiotic treatment failure for non-purulent SSTIs in the ED. We observed a high hospital admission rate and practice variability regarding antimicrobial agent and route. Tachypnea at triage, chronic ulcers, history of MRSA colonization or infection and cellulitis within the past year were independently associated with oral antibiotic treatment failure. Emergency physicians should consider these risk factors when deciding on oral versus intravenous antimicrobial therapy for patients with non-purulent SSTIs.

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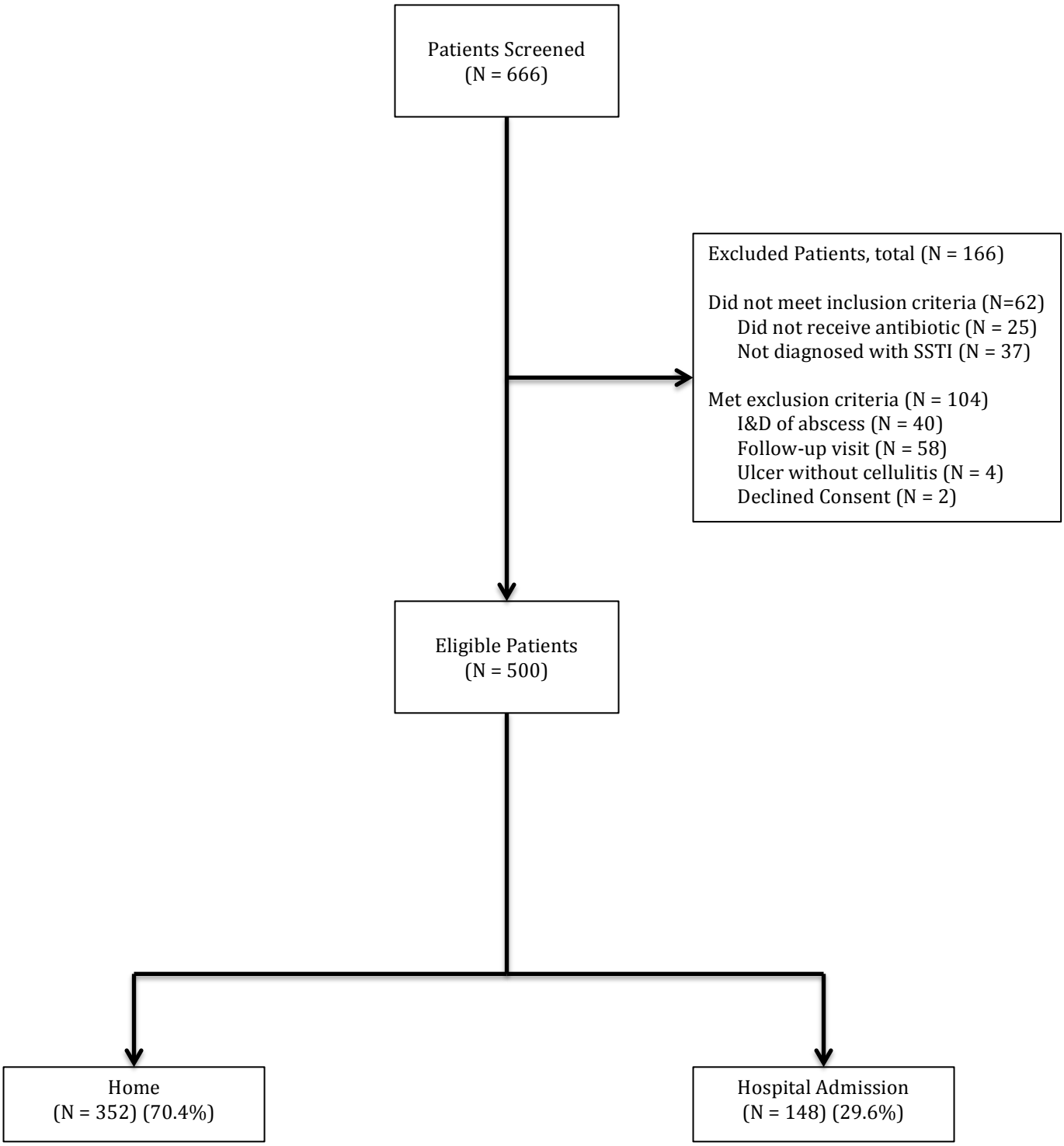
Figures

Figure 1. Flow Diagram of Patient Eligibility and Outcomes



Tables

Table 1. Baseline Characteristics of Adults with Nonpurulent Skin and Soft Tissue Infections seen in the Emergency Department (N=500)

Variable	N = 500
Age (years), mean ± SD	64 ± 19
Range	18 – 98
Male (%)	279 (55.8)
Hospital Site (%)	
TOH Civic Campus	278 (55.6)
TOH General Campus	222 (44.4)
Comorbidities	
Diabetes mellitus	126 (25.2)
Cellulitis in past 12 months	87 (17.4)
Coronary artery disease	58 (11.6)
Congestive heart failure	48 (9.6)
History of MRSA infection or colonization	43 (8.6)
Peripheral vascular disease	40 (8.0)
Liver disease	37 (7.4)
Chronic kidney disease	35 (7.0)
Active cancer	34 (6.8)
Lymphedema	33 (6.6)
Obesity	27 (5.4)
Injection drug use	14 (2.8)
Organ transplant recipient	4 (0.8)
Taking antibiotics at the time of ED presentation	
Oral	85 (17.0)
IV	13 (2.6)

SD = standard deviation; TOH = The Ottawa Hospital; MRSA = methicillin resistant *Staphylococcus aureus*; ED = emergency department; IV = intravenous

Table 2. Presenting Patient and Infection Characteristics (N=500)

Variable	N = 500
Triage Vital Signs	
Temperature, °C (mean ± SD)	36.6 ± 0.9
Heart Rate, beats/min (mean ± SD)	87 ± 19
Blood Pressure, mmHg (mean ± SD)	136 ± 24
Respiratory Rate, breaths/min (median, IQR)	18, 16 – 18
Oxygen Saturation, % (median, IQR)	97, 96 – 98
Infection Location (%)	
Leg	271 (54.2)
Foot	85 (17.0)
Arm	51 (10.2)
Hand	37 (7.4)
Face	29 (5.8)
Torso	22 (4.4)
Groin	5 (1.0)
Infection Characteristics (%)	
Chronic leg ulcers	56 (11.2)
Surgical site infection	30 (6.0)
Bite	12 (2.4)
Size	
TBSA <5%	401 (80.2)
TBSA 5 – 10%	97 (19.4)
TBSA >10%	2 (0.4)
Laboratory Tests	
White blood cell count ordered (%)	378 (75.6)
White blood cell count, $\times 10^9$/L (median, IQR)	9.2, 7 – 13

SD = standard deviation; IQR = interquartile range; TBSA = total body surface area

Table 3. Emergency Department Treatment (N=500)

Antibiotic Selection	**Number of patients, N=500 N (%)**
IV antibiotics only	339 (67.8)
Oral antibiotics only	146 (29.2)
Oral and IV antibiotics	15 (3.0)
Number of IV Antibiotics (N=354)	
One	281 (79.4)
Two	64 (18.1)
Three	9 (2.5)
Oral Antibiotics	
Cephalexin	121 (24.2)
Clindamycin	11 (2.2)
Amoxicillin-Clavulanate	9 (1.8)
Ciprofloxacin	7 (1.4)
Trimethoprim-Sulfamethoxazole	6 (1.2)
Doxycycline	4 (0.8)
Amoxicillin	3 (0.6)
IV Antibiotics	
Cefazolin	202 (40.4)
Ceftriaxone	80 (16.0)
Vancomycin	59 (11.8)
Piperacillin-Tazobactam	46 (9.2)
Clindamycin	40 (8.0)
Ciprofloxacin	3 (0.6)
Meropenem	3 (0.6)

IV = intravenous

Table 4. Antibiotic Treatment for 352 Patients Discharged from the ED

Outpatient Management	**Number of patients, N=352 N (%)**
Prescribed oral antibiotics	216 (61.4)
Prescribed IV antibiotics	130 (36.9)
Prescribed oral and IV antibiotics	6 (1.7)
Oral antibiotic in ED and sent home on oral antibiotic	146 (41.5)
IV antibiotic in ED and sent home on IV antibiotic*	136 (38.6)
IV antibiotic in ED and sent home on oral antibiotic	70 (19.9)
Intended location for outpatient IV antibiotics	
CCAC and OPAT clinic	99 (28.1)
CCAC only	26 (5.6)
ED	11 (2.2)
Oral antibiotics prescribed	222 (63.1)
Cephalexin	172 (48.9)
Clindamycin	19 (5.4)
Amoxicillin-Clavulanate	13 (3.7)
Trimethroprim-sulfamethoxazole	7 (2.0)
Ciprofloxacin	5 (1.4)
Doxycycline	5 (1.4)
Amoxicillin	1 (0.3)
IV antibiotics prescribed	136 (38.6)
Cefazolin	93 (26.4)
Ceftriaxone	31 (8.8)
Clindamycin	4 (1.1)
Vancomycin	3 (0.8)
Meropenem	1 (0.3)
Multiple IV Antibiotics	4(1.1)

IV = intravenous, CCAC = community care access centre; OPAT = outpatient parenteral antibiotic therapy; ED = emergency department

*6 patients were discharged with both intravenous and oral antibiotics

Table 5. Adverse Events for 352 Patients Discharged from the ED

Adverse Events	Number of patients, N = 352 N (%)
Return to the ED within 14 Days	143 (40.6)
Reason for return ED visit	
Repeat antibiotics	60 (17.0)
For SSTI and no admission	39 (11.1)
Unrelated medical problem	21 (6.0)
For SSTI and hospital admission	19 (5.4)
Diagnosed with abscess requiring I&D	4 (1.1)
Adverse device events	
Dislodged/blocked peripheral IV line	10 (2.8)
Other*	0 (0)
Adverse antibiotic events	
Nausea and/or vomiting	4 (1.1)
Rash	2 (0.6)
Diarrhea	2 (0.6)

*Other = thrombophlebitis, line infection or bacteremia
ED = emergency department; IV = intravenous; SSTI = skin and soft tissue infection; I&D = incision and drainage

Table 6. Outpatient Parenteral Antibiotic Therapy (OPAT) Clinic Data (N=85)

OPAT Clinic Metric	Number of patients, N = 85 N (%)
Cellulitis was the correct diagnosis**	82 (96.5)
Alternate diagnoses, total	
Gout	1
Lymphedema	1
Venous Stasis	1
Time to follow-up (days), median, IQR	4, 3 – 6
Number of visits, median, IQR	2, 1 – 3
Duration of IV antibiotics (days), median, IQR	7, 7 – 14
Duration of IV and oral antibiotics (days), median, IQR	19, 14 – 28

*A total of 99 patients were referred to the OPAT clinic from the emergency department
OPAT = outpatient parenteral antibiotic therapy; IV = intravenous; IQR = interquartile range

Table 7. Treatment Failure with Oral Antibiotics (N=85 of 288 Patients Treated with a Minimum of 48 Hours of Oral Therapy)

Oral Antibiotic Treatment Failures	Number of patients, N = 85 N (%)
Patient outcomes	
Switched to outpatient IV antibiotics	51 (60.0)
Hospitalized for IV antibiotics	30 (35.3)
Switched to outpatient oral antibiotics of different class	4 (4.7)
Treatment failure on initial ED visit*	68 (80.0)
Treatment failure on return ED visit within 14 days	17 (20.0)

*Patient was already on ≥48 hours of oral antibiotic therapy at time of index ED visit
IV = intravenous; ED = emergency department

Table 8. Predictors Associated with Oral Antibiotic Treatment Failure Using Multivariable Logistic Regression (N=288)

Predictor Variable	Adjusted OR	95% CI	P Value
Tachypnea at triage (RR>20)	6.31	1.80, 22.08	0.004
Chronic ulcers	4.90	1.68, 14.27	0.004
History of MRSA colonization or infection	4.83	1.51, 15.44	0.008
Cellulitis in the past 12 months	2.23	1.01, 4.96	0.05
Chronic kidney disease	2.60	0.82, 8.22	0.10
Diabetes mellitus	1.70	0.87, 3.32	0.12
The Hosmer-Lemeshow chi-square test yielded a p-value of 0.604 (χ^2 = 1.853, degrees of freedom = 3). C-statistic = 0.709. This indicates no evidence of poor fit.			

RR = respiratory rate; MRSA = methicillin resistant *Staphylococcus aureus*; OR = odds ratio; CI = confidence interval

Supplementary Appendix
Figure S1. Standardized Case Record Form

CASE #: _____ Abstractor Last Name: _____

Does this case meet INCLUSION criteria? ☐Yes ☐No (if 'No', stop here)

- Inclusion Criteria:
  - Age ≥ 18 years
  - Diagnosed with SSTI (cellulitis or erysipelas)
  - Prescribed/received an antibiotic for SSTI

Does this case meet EXCLUSION criteria? ☐Yes ☐No (if 'Yes', stop here)

- Exclusion Criteria:
  - Incision and drainage of an abscess
  - Follow-up visit (i.e. not the index visit for this SSTI)
  - Infected ulcer with no cellulitis

Demographics
Hospital: ❑TOH Civic ❑TOH General
Gender: ❑Male ❑Female
Date of birth: _____/____/____ (Y/M/D)
Date of index ED visit: _____/____/____ (Y/M/D)

Past Medical History (❑None of below)
❑Active Cancer (on chemotherapy or palliative)
❑Chronic kidney disease
❑Chronic venous insufficiency
❑Congestive heart failure
❑Coronary artery disease
❑ Corticosteroids (systemic)
❑Diabetes
❑Hepatic disease
❑ HIV
❑Intravenous drug use (IVDU)
❑Lymphedema/Venous Stasis
❑MRSA positive
❑Obesity
❑Organ transplant recipient
❑Peripheral vascular disease
❑Prior cellulitis

Infection Characteristics

Location of cellulitis: ❑Arm ❑Leg ❑Hand ❑Foot
❑Torso ❑Groin ❑Axilla ❑Face

Chronic ulcers: ❑Yes ❑No
Surgical site infection: ❑Yes ❑No
Bite (human or animal) ❑Yes ❑No

Maximum length of erythema (cm): _____ ❑Not recorded
Maximum width of erythema (cm): _____ ❑Not recorded
Area of erythema (cm^2): _____ ❑Not recorded
Area determined by: ❑Diagram ❑Photograph
❑Text (dimensions) ❑Text (non-specific)

Percent TBSA involved: ❑<5% ❑5–10% ❑10–20% ❑>20%

Triage Vital Signs

Temperature: _____ °C
Heart rate: _____ bpm
Respiratory rate: _____ breaths/minute
Systolic BP: _____ mmHg
SaO_2: _____ % ❑RA ❑Supplemental O_2

WBC Count: _____ ($x10^9$/L)

Current Treatment (Prior to ED Visit)

Is patient currently taking antibiotics for SSTI? ☐Yes ☐No

If yes, complete the following (check all that apply):
Antibiotic patient is currently taking:

❑PO Amoxicillin-Clavulanate (Clavulin) ❑PO Amoxicillin
❑PO TMP-SMX (Septra) ❑PO Cephalexin (Keflex)
❑PO Clindamycin ❑PO Ciprofloxacin
❑PO Penicillin
❑IV Ceftriaxone ❑IV Cefazolin (Ancef)
❑IV Clindamycin ❑IV Pipercillin-Tazobactam
❑IV Vancomycin ❑IV Penicillin
❑IV Ciprofloxacin ❑IV Meropenem
❑Other: _____

Duration (from start to ED visit; days): _____

ED Treatment (*what was given in the ED)*

Route:

- ❑Oral Antibiotics only?
- ❑IV Antibiotics only?
- ❑Oral and IV Antibiotics?

Number of Oral Antibiotics: ❑0 ❑1 ❑2

Number of IV Antibiotics: ❑0 ❑1 ❑2

Oral Cephalexin (Keflex)? ❑Yes ❑No

If Yes, Dose (mg): ❑250 ❑500 ❑1000

Oral Amoxicillin-Clavulanate? ❑Yes ❑No

If Yes, Dose (mg): ❑500 ❑875

Oral Amoxicillin? ❑Yes ❑No

If Yes, Dose (mg): ❑250 ❑500 ❑1000

Oral Clindamycin? ❑Yes ❑No

If Yes, Dose (mg): ❑300 ❑450 ❑600

Oral TMP-SMX (Septra)? ❑Yes ❑No

If Yes, Dose (mg): ❑800 (1 DS tab) ❑1600 (2 DS tabs)

Oral Ciprofloxacin? ❑Yes ❑No

If Yes, Dose (mg): ❑250 ❑500 ❑1000

IV Cefazolin (Ancef)? ❑Yes ❑No

If Yes, Dose (mg): ❑500 ❑1000 ❑1500 ❑2000

IV Ceftriaxone? ❑Yes ❑No

If Yes, Dose (mg): ❑1000 ❑1500 ❑2000

IV Clindamycin? ❑Yes ❑No

If Yes, Dose (mg): ❑300 ❑450 ❑600 ❑900

IV Meropenem? ❑Yes ❑No

If Yes, Dose (mg): ❑500 ❑1000 ❑1500 ❑2000

IV Vancomycin? ❑Yes ❑No

If Yes, Dose (mg): ❑500 ❑1000 ❑1500 ❑2000

IV Piperacillin-Tazobactam? ❑Yes ❑No

If Yes, Dose (mg): ❑3375 ❑4500

IV Ciprofloxacin? ❑Yes ❑No

If Yes, Dose (mg): ❑200 ❑400

What was ED patient disposition?
❑Home ❑ Hospital admission (If admitted, length of stay (days): _____)

If sent home: Where will patient get subsequent IV doses?
❑OPAT/CCAC ❑ CCAC only ❑ Return to ED ❑No IV ABX

<u>If sent home: ED Prescription:</u>

Oral Cephalexin (Keflex)? ❑Yes ❑No
If Yes, Dose (mg): ❑250 ❑500 ❑1000
Frequency: ❑BID ❑TID ❑QID
Duration (days): _____

Oral Amoxicillin-Clavulanate? ❑Yes ❑No
If Yes, Dose (mg): ❑500 ❑875
Frequency: ❑BID ❑TID ❑QID
Duration (days): _____

Oral Amoxicillin? ❑Yes ❑No
If Yes, Dose (mg): ❑250 ❑500 ❑1000
Frequency: ❑BID ❑TID ❑QID
Duration (days): _____

Oral Clindamycin? ❑Yes ❑No
If Yes, Dose (mg): ❑300 ❑450 ❑600
Frequency: ❑BID ❑TID ❑QID
Duration (days): _____

Oral TMP-SMX (Septra)? ❑Yes ❑No
If Yes, Dose (mg): ❑800 (1 DS tab) ❑1600 (2 DS tabs)
Frequency: ❑OD ❑BID ❑TID
Duration (days): _____

Oral Ciprofloxacin? ❑Yes ❑No
If Yes, Dose (mg): ❑250 ❑500 ❑1000
Frequency: ❑OD ❑BID ❑TID
Duration (days): _____

IV Cefazolin (Ancef)? ❑Yes ❑No
If Yes, Dose (mg): ❑500 ❑1000 ❑1500 ❑2000
Frequency: ❑BID ❑TID ❑QID
Duration (days): _____

IV Ceftriaxone? ❑Yes ❑No
If Yes, Dose (mg): ❑1000 ❑1500 ❑2000
Frequency: ❑OD ❑BID
Duration (days): _____

IV Clindamycin? ❑Yes ❑No
If Yes, Dose (mg): ❑300 ❑450 ❑600 ❑900
Frequency: ❑BID ❑TID ❑QID
Duration (days): _____

IV Meropenem? ❑Yes ❑No
If Yes, Dose (mg): ❑500 ❑1000 ❑1500 ❑2000
Frequency: ❑BID ❑TID ❑QID
Duration (days): _____

IV Vancomycin? ❑Yes ❑No
If Yes, Dose (mg): ❑500 ❑1000 ❑1500 ❑2000
Frequency: ❑OD ❑BID ❑TID
Duration (days): _____

IV Piperacillin-Tazobactam? ❑Yes ❑No
If Yes, Dose (mg): ❑3375 ❑4500
Frequency: ❑BID ❑TID ❑QID
Duration (days): _____

IV Ciprofloxacin? ❑Yes ❑No
If Yes, Dose (mg): ❑200 ❑400
Frequency: ❑BID ❑TID ❑QID
Duration (days): _____

If sent home: Return to ED within 14 days: ☐Yes ☐No

If yes (choose ONE only):

☐ Return to ED for SSTI and hospital admission

☐ Return to ED for SSTI but no admission

☐ Return to ED with abscess (If yes, I&D performed? ☐Yes ☐No)

☐Return to ED for repeat antibiotics: number of subsequent visits _____

☐ Return to ED for unrelated medical problem

If sent home: Changes to treatment in ED at repeat visit: ☐Yes ☐No ❑N/A

If yes (choose ONE only):

☐ Change from PO to IV antibiotics (name of new antibiotic:_____)

☐ Change to different PO antibiotic (name of new antibiotic:_____)

☐ Change to different IV antibiotic (name of new antibiotic:_____)

☐ Change to different antibiotic dose (new dose: ____ ____ ____ ____ mg)

If treatment was altered, reason for change in treatment plan:

☐ Worsening infection ☐ No improvement

☐ Vomiting ☐ Diarrhea ☐ Rash/hives

☐ Other Indicate: _____

<u>PO Treatment Failure?</u> ❑Yes ❑No

If yes, reason for treatment failure (check all that apply):

❑ Step-up from PO to IV antibiotic

❑ Change in class of antibiotic (due to worsening infection)

❑ Initial outpatient management with subsequent hospital admission

<u>IV Treatment Failure?</u> ❑Yes ❑No

If yes, reason for treatment failure (check all that apply):

❑ Change in class of antibiotic (due to worsening infection)

❑ Initial outpatient management with subsequent hospital admission

If sent home, Adverse Events:

Adverse drug reaction: ❑Yes ❑No

If yes: ❑Rash
❑ Nausea only (no vomiting)
❑ Vomiting
❑ Diarrhea
❑ Other: _____

Adverse device event: ❑Yes ❑No

If yes: ❑Blocked peripheral IV
❑Dislodged peripheral IV
❑Line thrombosis
❑Line infection

Subsequent hospital admission at 14 days from index ED visit? ❑Yes ❑No

If yes: ❑For worsening SSTI
❑For unrelated medical problem (specify:_____)

If referred to OPAT Clinic (❑Yes ❑No [STOP here]**):**

Did patient attend OPAT appointment? ❑Yes ❑No – lost to follow-up

Cellulitis was correct diagnosis: ❑Yes ❑No

If NO – specify alternate diagnosis: _____

Number of days from initial ED visit to first OPAT appointment: _____

Total number of visits to OPAT clinic: _____

Total number of days on IV antibiotics: _____

Total number of days on IV and PO antibiotics: _____ (❑N/A)

Table S1. Variable Definitions

Variable	Definition
Active cancer	Cancer being treated with chemotherapy or palliative; documented on ED ROT or recent consult
Chronic kidney disease	Impaired renal function ≥ 3 months. CKD should be charted on either ED record of treatment (ROT) or recent consult
Chronic venous insufficiency	Duplex ultrasound showing venous reflux (reversed flow for >0.5 seconds) or charted on the ED ROT or recent consult
Congestive heart failure	Documented on ROT or recent consult.
Coronary artery disease	Prior myocardial infarction, percutaneous coronary intervention or as otherwise stated on cardiology consult, ED ROT or recent consult
Corticosteroids (systemic)	Patient taking oral or intravenous corticosteroids at the time of ED visit
Diabetes mellitus	Taking insulin or oral medications (e.g. metformin, gliclazide, etc.) at the time of ED presentation, or documented on recent consult or ED ROT
Hepatic disease	Documentation on ED ROT or recent consult of any of the following: hepatitis B, hepatitis C or liver cirrhosis from any cause
Injection drug use	Documentation on ED ROT or recent consult of either intravenous or subcutaneous injection of medications or recreational drugs
Lymphedema	Documented on ED ROT or recent consult
MRSA positive	Documented on electronic health record to have known MRSA colonization or prior MRSA infection in the past 12 months
Obesity	Documented on ED ROT or recent consult
Organ transplant recipient	Documented on ED ROT, operative reports or a recent consult. Includes following transplants: heart, liver, kidney, and bone marrow
Peripheral vascular disease	Operative report of bypass grafting for peripheral vascular disease, or documented on ED ROT or recent consult
Prior cellulitis	Documented ED visit for non-purulent cellulitis or erysipelas in the past 12 months
Recent consult	Consult on electronic health record within 3 months of the patient's index ED visit

Table S2. Univariate Association with Oral Antibiotic Treatment Failure for 288 ED Patients Treated with a Minimum of 48 Hours of Oral Therapy

Variable	Oral Antibiotic Treatment Failure (N = 85)	No Oral Antibiotic Treatment Failure (N = 203)	P Value*
Age, years (mean ± SD)	67 ± 19	63 ± 20	0.15
Male gender (%)	48 (56.5)	110 (54.2)	0.72
Comorbidities (%)			
Chronic kidney disease	8 (9.4)	7 (3.4)	0.04
Congestive heart failure	8 (9.4)	10 (4.9)	0.15
Coronary artery disease	12 (14.1)	17 (8.4)	0.14
Diabetes mellitus	23 (27.1)	32 (15.8)	0.03
Hepatic disease	5 (5.9)	12 (5.9)	0.99
Intravenous drug use	3 (3.5)	1 (0.5)	0.09
Lymphedema	5 (5.9)	9 (4.4)	0.56
Obesity	3 (3.5)	5 (2.5)	0.69
Peripheral vascular disease	5 (5.9)	12 (5.9)	0.99
History of MRSA infection	11 (12.9)	5 (2.5)	0.001
Prior cellulitis in past 12 months	19 (22.4)	19 (9.4)	0.003
Vital Signs			
Temperature, °C (mean ± SD)	36.6 ± 0.8	36.3 ± 0.7	0.01
Heart Rate, beats/min (mean ± SD)	84 ± 17	83 ± 16	0.68
Blood Pressure, mmHg (mean ± SD)	140 ± 22	138 ± 24	0.69
Respiratory Rate, breaths/min (median, IQR)	16, 16 – 18	16, 16 – 18	0.85
Oxygen Saturation, % (median, IQR)	97, 96 – 98	97, 96 – 98	0.11
Infection Characteristics (%)			
Chronic Ulcers	13 (15.3)	7 (3.4)	0.0003
Bite	1 (1.2)	7 (3.4)	0.44
Surgical Site Infection	7 (8.2)	13 (6.4)	0.58
Size: TBSA ≥5%	14 (16.5)	25 (12.3)	0.35

*Using Chi Squared or Fisher's Exact Test for categorical variables; t-tests for normally distributed continuous variables; Wilcoxon tests for non-normally distributed continuous variables
SD = standard deviation; IQR = interquartile range; MRSA = methicillin resistant *Staphylococcus aureus*; TBSA = total body surface area

Table S3. Treatment Failure with IV Antibiotics (N=12 of 212 Patients Treated with a Minimum of 48 Hours of IV Therapy)

IV Antibiotic Treatment Failures	Number of patients, N = 12 N (%)
Patient Outcomes	
Hospitalized for IV antibiotics	11 (91.7)
Switched to outpatient IV antibiotics	1 (8.3)
Treatment failure on initial ED visit*	5 (41.7)
Treatment failure on return ED visit within 14 days	7 (58.3)

*Patient was already on ≥48 hours of IV antibiotic therapy at time of index ED visit
IV = intravenous; ED = emergency department

Table S4. Secondary Analysis Comparing Oral versus Intravenous Antibiotic Groups for Categorical Variables for all 500 Patients

Variable (n)	Oral Antibiotic Group Frequency, n (%) (n = 288)	IV Antibiotic Group Frequency, n (%) (n = 212)	P Value*
Male (279)	158 (54.9)	121 (57.1)	0.62
Chronic Ulcers (56)	20 (6.9)	36 (17.0)	0.0004
Surgical Site Infection (30)	20 (6.9)	10 (4.7)	0.30
Bite (12)	8 (2.8)	4 (1.9)	0.52
>5% TBSA (99)	39 (13.5)	60 (28.3)	<0.0001
Coronary artery disease (58)	29 (10.1)	29 (13.7)	0.21
Congestive heart failure (48)	18 (6.2)	30 (14.1)	0.003
Chronic kidney disease (35)	15 (5.2)	20 (9.4)	0.07
Chronic venous insufficiency (10)	8 (2.8)	2 (0.9)	0.20
Diabetes mellitus (126)	55 (19.1)	71 (33.5)	0.0002
Hepatic Disease (37)	17 (5.9)	20 (9.4)	0.14
HIV (8)	2 (0.7)	6 (2.8)	0.08
IVDU (14)	4 (1.4)	10 (4.7)	0.02
Lymphedema (33)	14 (4.9)	19 (9.0)	0.07
MRSA History (43)	16 (5.6)	27 (12.7)	0.005
Obesity (27)	8 (2.8)	19 (9.0)	0.002
Prior cellulitis (87)	38 (13.2)	49 (23.1)	0.004
PVD (40)	17 (5.9)	23 (10.8)	0.04
On Supplemental O_2 (36)	12 (4.2)	24 (11.7)	0.002

*Using Chi-Squared or Fisher's Exact Test

IV = intravenous; TBSA = total body surface area; HIV = human immunodeficiency virus; IVDU = intravenous drug use; MRSA = methicillin resistant *Staphylococcus aureus*; PVD = peripheral vascular disease

Table S5. Secondary Analysis Comparing Oral versus Intravenous Antibiotic Groups for Continuous Variables for all 500 Patients

Variable (n)	Oral Antibiotic Group Frequency, n (%) (N = 288)	IV Antibiotic Group Frequency, n (%) (N = 212)	P Value*
Age (mean ± SD)	64.4 ± 20.0	64.3 ± 16.9	0.95
Systolic BP (mean ± SD)	139 ± 23	131 ± 25	0.0007
Heart rate (mean ± SD)	84 ± 16	90 ± 21	<0.0001
Temperature (mean ± SD)	36.4 ± 0.8	36.8 ± 1.2	<0.0001
Respiratory Rate (median, IQR)	16 (16 – 18)	18 (16 – 20)	0.02
SaO_2 (median, IQR)	97 (96 – 98)	97 (96 – 98)	0.88
WBC count (median, IQR)	8.2 (6.6 – 11.2)	10.4 (7.7 – 14.7)	<0.0001

*Using t-tests for normally distributed variables, Wilcoxon tests for non-normally distributed variables

SD = standard deviation; IQR = interquartile range; IV = intravenous; BP = blood pressure; HR = heart rate; SaO_2 = oxygen saturation; WBC = white blood cell

Chapter Four: Outpatient Parenteral Antibiotic Therapy Following Emergency Department Treatment of Non-Purulent Skin and Soft Tissue Infections

Chapter Overview

In the previous chapter, we identified potential predictors associated with oral antibiotic treatment failure for non-purulent skin and soft tissue infections. Most patients in this study cohort received at least one dose of intravenous antibiotic, and more than one third of discharged patients were prescribed outpatient parenteral antibiotic therapy. Due to the study design, it was not possible to identify emergency physician rationale for selecting intravenous therapy, which is an important first step in the decision to refer to an outpatient parenteral antibiotic therapy program. Furthermore, it was not possible to describe outpatient parenteral antibiotic therapy clinic processes or to determine patient satisfaction with this treatment approach.

The following is a manuscript prepared for publication based on a prospective observational cohort study. The objectives of the manuscript were: 1) describe the performance of an emergency department-to-outpatient parenteral antibiotic therapy clinic program in the treatment of adults with non-purulent skin and soft tissue infections; 2) identify emergency physician rationale for selecting intravenous therapy; and 3) determine patient satisfaction with this treatment approach.

In **Appendix A** a copy of the approval letter from the Ottawa Health Science Network Research Ethics Board is provided.

Dr. Krishan Yadav is the first author of this manuscript and was responsible for the study development, data collection, data analysis and writing of the manuscript. This manuscript was co-authored by Dr. Ian Stiell, Dr. Kathryn Suh and Dr. George Wells. Dr. Debra Eagles and Dr. Venkatesh Thiruganasambandamoorthy provided valuable feedback throughout the process.

Outpatient Parenteral Antibiotic Therapy Following Emergency Department Treatment of Non-Purulent Skin and Soft Tissue Infections

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Abstract

Introduction

Emergency department (ED) patients with non-purulent skin and soft tissue infections (SSTIs) requiring intravenous antibiotics may be managed via outpatient parenteral antibiotic therapy (OPAT). To date, there are no prospective studies describing the performance of an ED-to-OPAT clinic program. Furthermore, there are no studies that have examined physician rationale for intravenous therapy, despite this being a critical first step in the decision to refer to an OPAT program. The primary objective was to determine the OPAT treatment failure rate for adults with non-purulent SSTIs who are initially managed in the ED.

Methods

We conducted a prospective observational cohort study of adults (age ≥ 18 years) with non-purulent SSTIs receiving parenteral therapy at two tertiary care EDs. Patients were excluded if they had purulent infections or could not provide consent. OPAT treatment failure was defined a priori as hospitalization after a minimum of 48 hours of OPAT for: (i) infection progression; (ii) line-related complications (e.g. bacteremia, thrombophlebitis, venous thromboembolism); or (iii) drug-related complications (e.g. *Clostridium difficile* colitis). Secondary outcomes were to describe OPAT clinic processes and adverse events, assess patient satisfaction, and identify ED physician rationale for selecting intravenous antibiotics. The emergency physician completed a form documenting rationale for intravenous therapy,

infection size and choice of antimicrobial agent, dose and duration. Patient satisfaction was assessed at a 14-day telephone follow up.

Results

We enrolled a consecutive sample of 153 patients (mean age 60 years, 82 male (53.6%) and 38 (24.8%) with diabetes). A total of 137 patients (89.5%) attended their OPAT clinic appointment. Of the 101 patients prescribed cefazolin, 50.5% received 1000 mg and 48.5% received 2000 mg. There were low rates of OPAT treatment failure (4.4%). None of the adverse peripheral intravenous line events (10.9%) and adverse antibiotic events (8.0%) required hospitalization. Patients reported a high degree of satisfaction with timeliness of clinic referral (median score 9 out of 10) and overall care received (median score of 10 out of 10). The top 5 reasons given by physicians for selecting intravenous therapy were: clinical impression of severity (52.9%); failed oral antibiotic therapy (41.8%); diabetes (17.6%); severe pain (7.8%); and peripheral vascular disease (7.8%).

Conclusion

This is the first study to identify physician rationale for the use of intravenous antibiotics for SSTIs. There was significant variability in antibiotic prescribing practices by ED physicians. This prospective study demonstrates that an ED-to-OPAT clinic program for non-purulent SSTIs is safe, has a low rate of treatment failures and results in high patient satisfaction.

Introduction

First described in 1974, outpatient parenteral antibiotic therapy (OPAT) is defined as the administration of at least two doses of parenteral antimicrobials on different days without interim observation.[1] OPAT is an attractive option for adults with non-purulent skin and soft tissue infections (SSTIs) who require intravenous antibiotics. Patients discharged from the emergency department (ED) can receive OPAT follow up in a number of settings: return to the ED, a family physician clinic, a homecare clinic run by nurses, or a dedicated OPAT clinic. Due to difficulties with primary care access[2] and associations between ED overcrowding and increased adverse events[3], an ED-to-OPAT clinic program may be a preferred option due to important advantages: 1) decreased hospital admissions; 2) increased patient convenience; and 3) decreased ED visits.

ED-based studies have shown that intravenous antibiotics are frequently administered[4,5] and that antibiotic overuse is common.[6] Surprisingly, there is scant literature regarding ED antibiotic prescribing for SSTIs.[7-9] Furthermore, there are no published studies describing ED physician rationale for selecting intravenous over oral antibiotics, despite this being a critical first step in the development of an OPAT program.[1,8]Administration of OPAT is not without risk. Potential adverse events for any infection treated with OPAT include infection progression, peripheral line-related complications or adverse antibiotic events that may warrant subsequent hospitalization.[9,10] Prior studies report the hospital admission rate following OPAT ranging from 2.6 to 8%.[9,11,12] However, these studies included a number of

infections, making it difficult to determine the true clinical failure rate for SSTIs in particular. A recent retrospective study reported a hospital admission rate of 5.5% for a cellulitis OPAT cohort, although the reasons for hospitalization were not described.[13]

The primary objective of this study was to determine the OPAT treatment failure rate for adults with non-purulent SSTIs who are initially managed in the ED. Secondary objectives were to describe OPAT clinic processes (time to first appointment, total number of clinic visits and duration of therapy), adverse events, assess patient satisfaction, and identify emergency physician rationale for selecting intravenous antibiotics,

Methods

Study Design and Setting

We conducted a prospective observational cohort study of adult patients with non-purulent SSTIs initially managed in the ED with intravenous antibiotics and referred to the OPAT clinic. The study population was enrolled from the Ottawa Hospital Civic and General EDs (two tertiary care adult EDs with a combined 170,000 patient visits annually). All enrolled patients were referred to the OPAT clinic, located at the Ottawa Hospital Civic Campus. The Ottawa Hospital OPAT clinic was established in 2014 and operates on three half days per week by appointment only. The Ottawa Health Science Network Research Ethics Board approved this study.

Study Population

We enrolled a consecutive sample of patients meeting eligibility criteria from January 15 to June 20, 2017. Eligible patients were adults (age ≥ 18 years) presenting to the ED and diagnosed with a non-purulent SSTI that was felt by the emergency physician to require intravenous antibiotics and follow up in the OPAT clinic. Patients were excluded for the following reasons: (i) age < 18 years; (ii) diagnosis of a purulent SSTI where an incision and drainage procedure was performed; (iii) necrotizing infections; (iv) significant cognitive or verbal impairment such that informed consent was not feasible; or (v) those who were not local residents or who did not have a telephone.

Intravenous Antibiotic Treatment

The emergency physician selected the agent, dose, frequency and duration of parenteral antibiotic at their own discretion. All patients received intravenous antibiotics in the community via the local homecare program. Patients returned to the ED for subsequent intravenous doses if there was a delay in establishing homecare as an outpatient. Patients then followed up with an infectious disease specialist at the OPAT clinic, at the next available clinic date (ranging from two to ten days). The infectious disease specialist was responsible for determining if further intravenous therapy was warranted or if the patient could be stepped down to oral therapy.

Data Collection

All patients were assessed by emergency physicians or residents supervised by attending emergency physicians. Study details were distributed by electronic mail to familiarize physicians with the study. The emergency physician was responsible for

completing the OPAT referral form (see the supplementary appendix), which also required the physician to indicate rationale for selecting intravenous therapy. Physicians were asked to use a ruler on the right-margin of the referral form to obtain accurate infection dimensions. Patients were provided with an information sheet outlining the study details and verbal consent was obtained for a 14-day telephone follow-up call. The principal investigator (KY) screened all referrals to the OPAT clinic to ensure that no cases were missed.

All patients received a 14-day telephone follow up to assess patient satisfaction. Participants were considered lost to telephone follow up if they could not be reached after a maximum of three phone calls. The principal investigator abstracted all relevant clinical data from the electronic health record (ED physician and nursing notes, OPAT clinic records) onto a standardized case record form (see the supplementary appendix). Eligible patients were enrolled regardless of whether the OPAT referral form was fully completed.

Outcome Measures

The primary outcome was OPAT treatment failure. There is no established definition of OPAT treatment failure for SSTIs in the literature. The United States Food and Drug Administration recommends that clinical response to treatment should be assessed at 48 to 72 hours from initiating therapy.[14] When surveyed, a majority of Canadian emergency physicians selected 48 hours as the optimal timeframe for determining if treatment failure had occurred following initiation of antibiotic therapy.[15] After review of the literature[4,5,16-20] and discussion with local

experts in emergency medicine and infectious disease, we devised a definition of OPAT treatment failure. Patients were considered to have a treatment failure if a patient was subsequently admitted to hospital after a minimum of 48 hours of OPAT for any of the following reasons: (i) worsening infection; (ii) line-related complications (e.g. bacteremia, venous thrombosis); or (iii) drug-related complications (e.g. *Clostridium difficile* colitis).

Secondary outcomes included ED physician rationale for selecting the intravenous route, OPAT clinic data and patient satisfaction. The treating physician was allowed to select more than one reason for selecting intravenous therapy. For clinic data, we recorded time to first visit, total number of visits, and the number of patients lost to follow-up. At a 14-day telephone follow up, we asked patients to give a numerical rating from one (least satisfied) to ten (most satisfied) with respect to timeliness of referral from the ED and overall patient satisfaction. Adverse outcomes included antibiotic events and device events.

Data Analysis

We used descriptive statistics to describe the proportion of patients who had an OPAT treatment failure, adverse antibiotic or device events, OPAT clinic data and patient satisfaction. Continuous data are presented as means with standard deviations or medians with an interquartile range (IQR, Q1 – Q3) for normally and non-normally distributed data, respectively. Categorical data are presented as proportions with 95% confidence intervals.

Sample Size

The OPAT clinic at the Ottawa Hospital treats approximately 30 new patients with SSTIs per month. After adjusting for 10% drop out, we estimated a consecutive enrolment of approximately 135 patients over a 5-month period. This sample size was based on feasibility due to funding and time constraints.

Results

We screened 214 cases referred to the OPAT clinic over the five-month study period and identified 153 eligible cases (Figure 1). A total of 137 patients (89.5%) attended their clinic appointment. Of the remaining 16 patients (10.5%), five patients were admitted to hospital prior to their clinic appointment and 11 were lost to follow up. For patients who attended their appointment, we were able to contact 118 patients (86.0%) for a 14-day telephone follow up.

Tables 1 and 2 highlight the baseline patient and infection characteristics, respectively. The mean age of enrolled patients was 60 years, and almost a quarter of patients had diabetes (24.8%) or lymphedema (23.5%). Almost half of patients (48.4%) were taking oral antibiotics at the time of their presentation to the ED. The most common location of infection was the leg (45.1%) and the median area of erythema was 150 cm^2 (IQR 40 – 300). Emergency physicians ordered blood tests in the majority of these patients (68.0%) and the median white blood cell count was 9.0×10^9/L (IQR 6.8 – 11.6). The treating physician ordered blood cultures for 22 patients (14.4%); there were clinically significant positive blood cultures (one positive blood culture was considered to be a contaminant).

Table 3 shows the variation in antimicrobial therapy administered in the ED. Most patients received a single intravenous antibiotic (93.5%). Cefazolin was the most commonly administered antibiotic and was administered in 99 patients (64.7%). Of those that received cefazolin, 33 patients (33.3%) and 66 patients (66.7%) received 1000 mg and 2000 mg, respectively.

In Table 4, the variation in antibiotic prescribing practices for patients sent home from the ED is presented. Cefazolin was the most commonly prescribed antibiotic (66.0%). The chosen dose of cefazolin for 101 patients was as follows: 1000 mg (n = 51, 50.5%); 1500 mg (n = 1, 1.0%); and 2000 mg (n = 49, 48.5%). After cefazolin, the most commonly prescribed antibiotics were ceftriaxone (19.6%) and clindamycin (10.5%).

Emergency physician rationale for selecting intravenous antibiotics is shown in Table 5. Treating physicians provided a total of 22 different rationales. The top five reasons for selecting intravenous therapy were: clinical impression (52.9%); failed oral antibiotic therapy (41.8%); diabetes (17.6%); severe pain (7.8%); and peripheral vascular disease (7.8%).

Of the total 153 patients referred to the OPAT clinic, 137 patients (89.5%) attended their scheduled appointment. The OPAT clinic data are shown in Table 6. The emergency physician and infectious disease specialist diagnosis of a non-purulent

SSTI were concordant in 93.4% of cases. The median time to the first clinic visit was 5 days (IQR 4 – 7). The median duration of intravenous therapy was 9 days (IQR 7 – 14). Patients reported a high degree of satisfaction with timeliness of clinic referral (median score 9 out of 10) and overall care received (median score of 10 out of 10). Of the 118 patients who could be reached for telephone follow up, 110 patients (93.2%) indicated they would prefer follow-up with the OPAT clinic if they required intravenous antibiotics in the future.

Table 7 shows 14-day outcomes for the 137 patients who attended their initial OPAT clinic appointment. The majority of patients (63.5%) returned to the ED within 14 days. The most common reason was a return for scheduled intravenous doses if the homecare program could not be initiated in time for the next required dose. Only six patients suffered an OPAT treatment failure (4.4%); all were due to worsening infection. Fifteen patients (10.9%) had an adverse device event (blocked or dislodged peripheral intravenous line) and there were no cases of line infection or bacteremia. Eleven patients (8.0%) had an adverse antibiotic event with the majority experiencing diarrhea. None of the adverse device or antibiotic events resulted in hospitalization.

Discussion

Interpretation of Results

This prospective observational cohort study describes ED-to-OPAT clinic performance in the management of adults with non-purulent SSTIs. There was

significant practice variation amongst emergency physicians regarding antibiotic agent, dose and duration. Cefazolin was the most commonly prescribed parenteral antibiotic and emergency physicians were split regarding the dose. This is the first study to prospectively evaluate emergency physician rationale for intravenous antibiotics. The top five reasons for selecting intravenous therapy were: clinical impression; failed oral antibiotic therapy; diabetes; severe pain; and peripheral vascular disease. There was a very low rate of both OPAT treatment failures and adverse antibiotic or peripheral line events. Patients reported a very high degree of satisfaction with their care. Our findings strengthen the argument that an ED-to-OPAT clinic model is effective, safe, and results in a high degree of patient satisfaction.

Previous Studies

Our study found a low OPAT treatment failure rate (4.4%) that is similar to previously published studies.[9,11,12] However, this is the first prospective study to assess OPAT for non-purulent SSTIs in particular. Appropriate patient selection for outpatient intravenous therapy is a critical first step to the success of an OPAT program.[1,8] However, there are no published studies to date that have examined physician rationale for selecting parenteral therapy. Current guidelines[1,21,22] list patient satisfaction as a key element to an OPAT program. We found a high degree of patient satisfaction that is similar to prior studies.[12,23]

Strengths

A consecutive sample of patients was enrolled and we screened all OPAT clinic referrals so as not miss any potential cases over the study period. The data were

collected prospectively and we were thus able to accurately identify physician rationale for selecting parenteral therapy. This is the first prospective study that provides important insight into physician decision-making regarding patient selection for intravenous therapy.

Limitations

There are study limitations that warrant mention. First, this study was conducted at two tertiary care EDs but had a small sample size due to feasibility. Some patients did not attend their clinic appointment and were lost to follow-up (7.2%). It is possible that some of these patients lost to follow up may have experienced a treatment failure. However, we feel it is unlikely that patients who received treatment at our centre would present to another hospital for further care. Another limitation was that 14.0% of patients who attended the clinic visit could not be reached by telephone or declined consent. It is possible that their patient satisfaction scores may have differed significantly from the group that had a complete follow up. Third, the confidence in the results may be affected by the small sample size.

A further limitation is that we could not record patient weight or categorize the degree of obesity due to feasibility in obtaining this data. It is possible that at least some of the variation observed in antimicrobial dosing, duration and frequency might be related to patient body habitus. However, we feel this is unlikely because the small proportion of patients with obesity (12.4%) would not fully explain the high degree of observed dosing variability.

Lastly, there is no validated definition of OPAT treatment failure. Petrak et al. recommended that future studies examining OPAT efficacy should include robust definitions for treatment failure.[11] We attempted to develop a robust definition by reviewing the literature[4,5,16-20] and reaching consensus among local experts in emergency medicine and infectious disease. This definition was a composite endpoint. Disadvantages of using a composite endpoint include misleading results if one component of the outcome heavily drives the result, especially if it is the least patient-important outcome. However, the components of our definition all resulted in the same final outcome of hospital admission.

Clinical Implications

There are important clinical implications that deserve mention. Our study demonstrated a high degree of variation in antimicrobial prescribing practices. While this may in part be due to variation in patient presentation (e.g. animal bite, antibiotic allergy), the results still reflect a lack of consensus amongst emergency physicians regarding optimal management of this common clinical condition. For example, the dose for the most commonly prescribed antibiotic (cefazolin) was nearly evenly split – which cannot be explained by heterogeneity in patient presentation alone. The rates of adverse events and OPAT treatment failure were very low, suggesting that the ED-to-OPAT clinic model is safe, effective and results in high patient satisfaction. This model can be introduced in other communities to potentially decrease hospital admissions and associated healthcare costs.

Research Implications

Our study identified reasons emergency physicians institute intravenous antibiotic therapy for non-purulent SSTIs. Future studies should seek to assess whether patients with these identified rationales truly require intravenous therapy, or whether they can be treated with less invasive and cheaper oral antibiotics. We also identified a large degree of variation with antibiotic prescription practices. Randomized clinical trials comparing various doses and durations of intravenous therapy will aid in making more robust guidelines to aid emergency physicians when selecting the appropriate antibiotic route.

Conclusion

This is the first study to identify physician rationale for the use of intravenous antibiotics for SSTIs. There was significant variability in antibiotic prescribing practices by ED physicians. This prospective study demonstrates that an ED-to-OPAT clinic program for non-purulent SSTIs is safe, has a low rate of treatment failures and results in high patient satisfaction.

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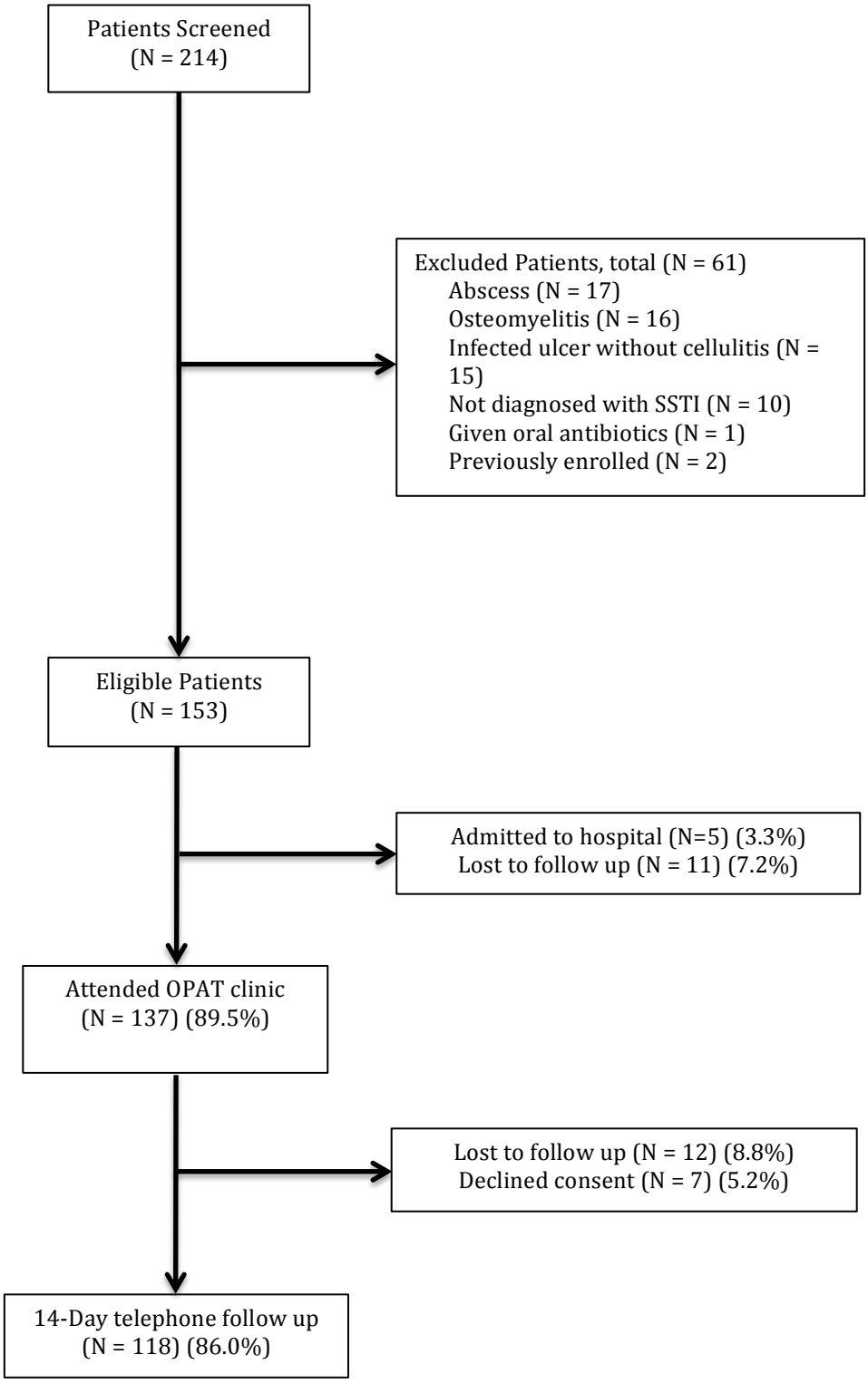
Figures

Figure 1. Flow Diagram



Tables

Table 1. Baseline Characteristics of Adults with Non-Purulent Skin and Soft Tissue Infections (SSTIs) seen in the ED (N = 153)

Variable	N = 153
Age (years), mean ± SD	60 ± 19
Range	21 – 100
Male (%)	82 (53.6)
Hospital Site (%)	
TOH Civic Campus	80 (52.3)
TOH General Campus	73 (47.7)
Comorbidities	
Diabetes mellitus	38 (24.8)
Lymphedema	36 (23.5)
Prior cellulitis in past 12 months	26 (17.0)
Obesity	19 (12.4)
Peripheral vascular disease	12 (7.8)
Coronary artery disease	10 (6.5)
Active cancer	8 (5.2)
Chronic kidney disease	8 (5.2)
Congestive heart failure	7 (4.6)
Liver disease	7 (4.6)
Injection drug use	7 (4.6)
History of MRSA colonization or infection	5 (3.3)
Organ transplant recipient	1 (0.6)
Medications	
Currently taking oral antibiotics	74 (48.4)

SD = standard deviation; TOH = The Ottawa Hospital; MRSA = methicillin resistant *Staphylococcus aureus*; IV = intravenous

Table 2. Presenting Patient and Infection Characteristics (N=153)

Variable	N = 153
Triage Vital Signs	
Temperature, °C (mean ± SD)	36.5 ± 0.7
Heart Rate, beats/min (mean ± SD)	86 ± 17
Blood Pressure, mmHg (mean ± SD)	138 ± 21
Respiratory Rate, breaths/min (mean ± SD)	17 ± 2
Oxygen Saturation, % (median, IQR)	97, 96 – 98
Infection Location (%)	
Leg	69 (45.1)
Foot	21 (13.7)
Arm	23 (15.0)
Hand	19 (12.4)
Face	16 (10.5)
Torso	5 (3.3)
Infection Characteristics (%)	
Chronic Leg Ulcers	20 (13.1)
Bite	11 (7.2)
Surgical Site Infection	4 (2.6)
Infection dimensions recorded (%)	124 (81.0)
Area of erythema, cm^2 (median, IQR)	150, 40 – 300
Laboratory Tests	
White blood cell count ordered (%)	104 (68.0)
White blood cell count, $\times 10^9$/L (median, IQR)	9.0, 6.8 – 11.6
Blood Culture Sent	22 (14.4)
Negative Blood Culture	21 (13.7)
Contaminant	1 (0.6)
Positive Blood Culture	0 (0)

SD = standard deviation; IQR = interquartile range; TBSA = total body surface area

Table 3. Intravenous Antibiotic Treatment Administered While in the ED (N=153)

Antibiotic Selection	Number of patients, N=153 N (%)
IV antibiotics only	148 (96.7)
Oral and IV antibiotics	5 (3.3)
Number of IV antibiotics	
One	143 (93.5)
Two	10 (6.5)
IV antibiotic agent and single dose	
Cefazolin	99 (64.7)
Dose = 1000 mg	33 (21.6)
Dose = 2000 mg	66 (43.1)
Ceftriaxone	37 (24.2)
Dose = 1000 mg	31 (20.3)
Dose = 2000 mg	6 (3.9)
Clindamycin	17 (11.1)
Dose = 300 mg	1 (0.6)
Dose = 600 mg	12 (7.8)
Dose = 900 mg	4 (2.6)
Vancomycin	5 (3.3)
Dose = 1000 mg	3 (2.0)
Dose = 1500 mg	1 (0.6)
Dose = 2000 mg	1 (0.6)
Piperacillin-Tazobactam (3375 mg)	2 (1.3)
Meropenem (1000 mg)	2 (1.3)
Ciprofloxacin (400 mg)	1 (0.6)
Oral antibiotics*	
Clindamycin	2 (1.3)
Ciprofloxacin	2 (1.3)
Trimethoprim-Sulfamethoxazole	1 (0.6)

IV = intravenous

*Given in addition to intravenous antibiotics

Table 4. Intravenous Antibiotic Prescriptions for Patients Discharged from the ED (N=153)

ED IV Antibiotic Prescription	Number of patients, N=153 N (%)
Cefazolin	101 (66.0)
Single Dose	
1000 mg	51 (33.3)
1500 mg	1 (0.6)
2000 mg	49 (32.0)
Frequency	
Twice daily	5 (3.3)
Three times daily	94 (61.4)
Four times daily	2 (1.3)
Duration, days (median, IQR)	7, 7 – 7
Range	3 – 14
Ceftriaxone	30 (19.6)
Single Dose	
1000 mg	25 (16.3)
2000 mg	5 (3.3)
Frequency	
Once daily	1 (0.6)
Twice daily	29 (19.0)
Duration, days (median, IQR)	7, 7 – 9
Range	3 – 10
Clindamycin	16 (10.5)
Single Dose	
300 mg	1 (0.6)
450 mg	1 (0.6)
600 mg	11 (7.2)
900 mg	3 (2.0)
Frequency	
Twice daily	1 (0.6)
Three times daily	15 (9.8)
Duration, days (median, IQR)	7, 7 – 7
Range	5 – 14
Vancomycin	3 (2.0)
Piperacillin-Tazobactam	2 (1.3)
Meropenem	2 (1.3)
Ciprofloxacin	1 (0.6)

IQR = interquartile range (Q1 – Q3); Range = min – max; IV = intravenous, ED = emergency department

Table 5. Emergency Physician Rationale for IV Antibiotics for all 153 Patients

Rationale for IV Antibiotics*	**Number of patients, N (%) N = 153**
Clinical Impression	81 (52.9)
Failed oral antibiotic therapy	64 (41.8)
Diabetes	27 (17.6)
Severe pain (>8/10)	12 (7.8)
Peripheral vascular disease	12 (7.8)
Bite	7 (4.6)
Prior SSTI that required IV antibiotics	5 (3.3)
Social/compliance issues	5 (3.3)
Abnormal skin at infection site**	3 (2.0)
Prior oral antibiotic failure	2 (1.3)
Prior SSTI in same area	2 (1.3)
Hypotension or fever and tachycardia	2 (1.3)
Rapidly spreading erythema or lymphangitis	2 (1.3))
Indwelling IV catheter	1 (0.6)
Blunt trauma	1 (0.6)
Ear involvement	1 (0.6)
Injection drug use	1 (0.6)
Immunocompromised	1 (0.6)

*Emergency physicians indicated >1 rationale for some patients
**Surgical site infection, underlying burn, underlying melanoma
IV = intravenous; SSTI = skin and soft tissue infection

Table 6. Outpatient Parenteral Antibiotic Therapy (OPAT) Clinic Data (N=137)

OPAT Clinic Metric	Number of patients, N (%) N = 137
Cellulitis confirmed as diagnosis*	128 (93.4)
Alternate diagnoses	
Abscess	3 (2.2)
Osteomyelitis	3 (2.2)
Drug rash	2 (1.4)
Stasis dermatitis	1 (0.7)
Time to follow-up (days), median, IQR	5, 4 – 7
Range	1 – 18
Total clinic visits, median, IQR	2, 1 – 3
Total Duration of IV antibiotics (days), median, IQR	9, 7 – 14
Total Duration of IV and oral antibiotics (days), median, IQR	17, 12 – 28
Patient follow up at 14 days	118 (86.1)
Patient satisfaction (scale of 1 to 10**)	
Timeliness of referral to OPAT clinic	9, 8 – 10
Overall satisfaction with care received	10, 9 – 10
Patient preference for follow up in future	
OPAT clinic	110 (80.3)
Family doctor	5 (3.6)
ED	3 (2.2)
Unknown (lost to follow up)	19 (13.9)

*The infectious disease specialist agreed with the emergency physician diagnosis of a non-purulent SSTI

**1 is least satisfied and 10 is most satisfied

OPAT = outpatient parenteral antibiotic therapy; IV = intravenous; IQR = interquartile range, Q1–Q3

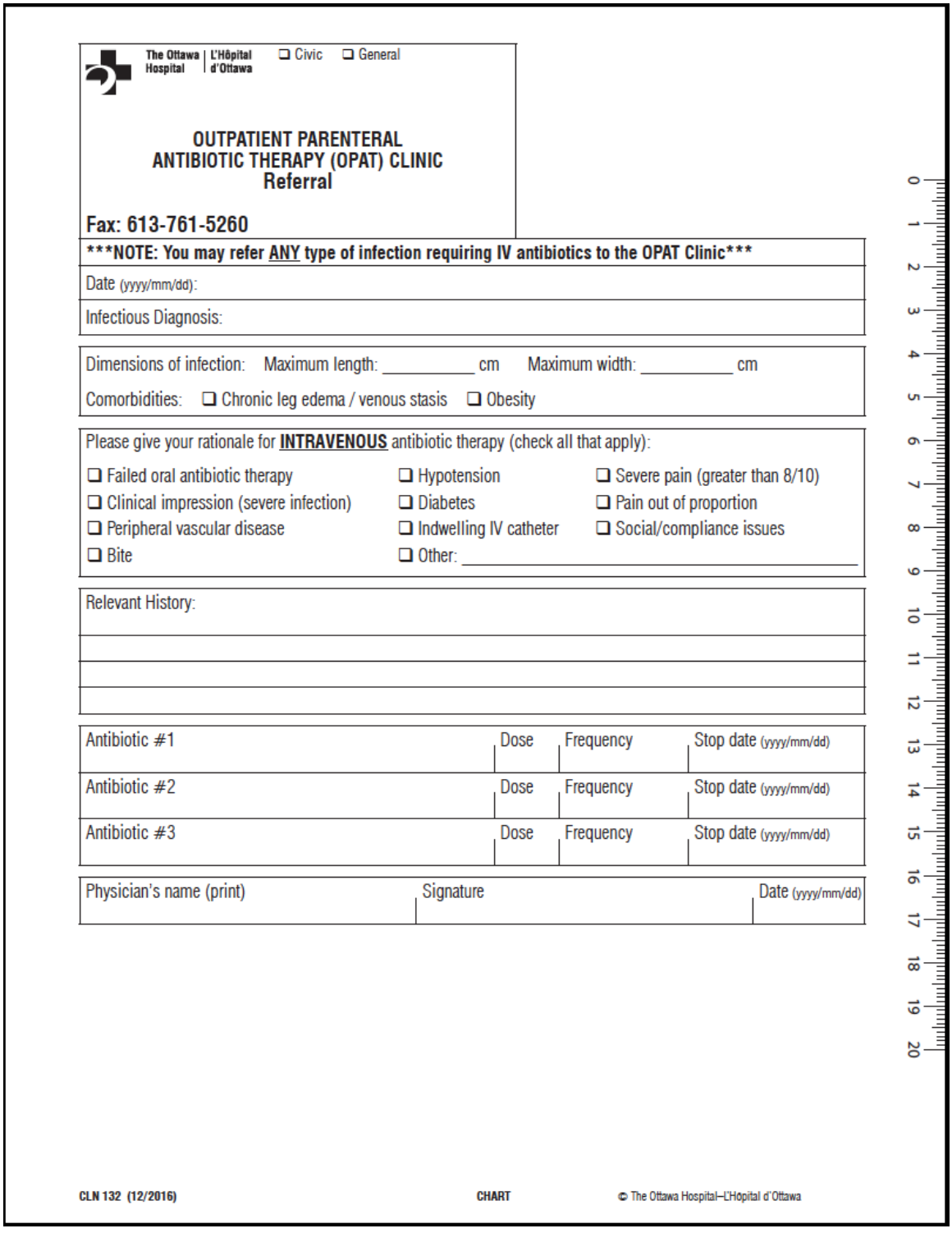
Table 7. Outcomes at 14 Days from Index ED Visit for 137 Patients Not Lost to Follow-up

Adverse Events	Number of patients, N = 137, N (%)
Reason for Return ED Visit Within 14 Days	
Repeat IV antibiotic doses	55 (40.1)
Number of repeat visits, median, IQR	1, 1 – 2
Range	1 – 5
For SSTI and discharged home	18 (13.1)
For SSTI and hospital admission (OPAT Treatment Failure)	6 (4.4)
Diagnosed with abscess requiring I&D	4 (2.9)
Unrelated medical problem	4 (2.9)
Adverse Device Events	15 (10.9)
Blocked peripheral IV line	9 (6.6)
Dislodged peripheral IV line	6 (4.4)
Thrombophlebitis, line infection or bacteremia	0 (0)
Adverse Antibiotic Events	11 (8.0)
Diarrhea	8 (5.8)
Rash	2 (1.4)
Oral thrush	1 (0.7)
Nausea and/or vomiting	0 (0)

IQR = interquartile range (Q1 – Q3); Range = min – max
ED = emergency department; IV = intravenous; SSTI = skin and soft tissue infection; I&D = incision and drainage

Supplementary Appendix

Figure S1. OPAT Clinic Referral Form



The Ottawa Hospital | L'Hôpital d'Ottawa ❑ Civic ❑ General

OUTPATIENT PARENTERAL ANTIBIOTIC THERAPY (OPAT) CLINIC Referral

Fax: 613-761-5260

NOTE: You may refer ANY type of infection requiring IV antibiotics to the OPAT Clinic

Date (yyyy/mm/dd):

Infectious Diagnosis:

Dimensions of infection: Maximum length: _____ cm Maximum width: _____ cm

Comorbidities: ❑ Chronic leg edema / venous stasis ❑ Obesity

Please give your rationale for **INTRAVENOUS** antibiotic therapy (check all that apply):

❑ Failed oral antibiotic therapy	❑ Hypotension	❑ Severe pain (greater than 8/10)
❑ Clinical impression (severe infection)	❑ Diabetes	❑ Pain out of proportion
❑ Peripheral vascular disease	❑ Indwelling IV catheter	❑ Social/compliance issues
❑ Bite	❑ Other: _____	

Relevant History:

Antibiotic	Dose	Frequency	Stop date (yyyy/mm/dd)
Antibiotic #1			
Antibiotic #2			
Antibiotic #3			

Physician's name (print)	Signature	Date (yyyy/mm/dd)

CLN 132 (12/2016) CHART

Figure S2. Standardized Case Record Form

CASE #: _____ Abstractor Last Name: _____

Demographics

Hospital: ❑TOH Civic ❑TOH General
Gender: ❑Male ❑Female
Date of birth: _____/____/____ (Y/M/D)
Date of index ED visit: _____/____/____ (Y/M/D)

Past Medical History (❑None of below)

❑Active Cancer (on chemotherapy or palliative)
❑Chronic kidney disease
❑Chronic venous insufficiency
❑Congestive heart failure
❑Coronary artery disease
❑ Corticosteroids (systemic)
❑Diabetes
❑Hepatic disease
❑ HIV
❑Intravenous drug use (IVDU)
❑Lymphedema/Venous Stasis
❑MRSA positive
❑Obesity
❑Organ transplant recipient
❑Peripheral vascular disease
❑Prior cellulitis

Infection Characteristics

Location of cellulitis: ❑Arm ❑Leg ❑Hand ❑Foot
❑Torso ❑Groin ❑Axilla ❑Face

Chronic ulcers: ❑Yes ❑No
Surgical site infection: ❑Yes ❑No
Bite (human or animal) ❑Yes ❑No

Maximum length of erythema (cm): _____ ❑Not recorded
Maximum width of erythema (cm): _____ ❑Not recorded
Area of erythema (cm^2): _____ ❑Not recorded
Area determined by: ❑Diagram ❑Photograph
❑Text (dimensions) ❑Text (non-specific)

Percent TBSA involved: ❑<5% ❑5–10% ❑10–20% ❑>20%

Triage Vital Signs

Temperature: _____ °C
Heart rate: _____ bpm
Respiratory rate: _____ breaths/minute
Systolic BP: _____ mmHg
SaO_2: _____ % ❑RA ❑Supplemental O_2

WBC Count: _____ ($x10^9$/L)
Blood Cultures sent? ☐Yes ☐No
If Yes: ☐Positive ☐Negative ☐Contaminated
If Positive: ☐MSSA ☐MRSA ☐Group A Strep
☐Pseudomonas ☐Proteus ☐Strep Pneumoniae
☐Serratia ☐Eikenella ☐Vibrio
☐H. influenzae ☐Contaminated

Current Treatment (Prior to ED Visit)

Is patient currently taking antibiotics for SSTI? ☐Yes ☐No
If yes, complete the following (check all that apply):
Antibiotic patient is currently taking:

❑PO Amoxicillin-Clavulanate (Clavulin)
❑PO Amoxicillin
❑PO TMP-SMX (Septra)
❑PO Cephalexin (Keflex)
❑PO Clindamycin
❑PO Ciprofloxacin
❑PO Penicillin
❑PO Doxycycline
❑IV Ceftriaxone
❑IV Cefazolin (Ancef)
❑IV Clindamycin
❑IV Pipercillin-Tazobactam
❑IV Vancomycin
❑IV Penicillin
❑IV Ciprofloxacin
❑IV Meropenem
❑Other: _____

Duration (from start to ED visit; days): _____

ED Treatment (*what was given in the ED)*

Route:

- ❑Oral Antibiotics only?
- ❑IV Antibiotics only?
- ❑Oral and IV Antibiotics?

Number of Oral Antibiotics: ❑0 ❑1 ❑2 ❑3

Number of IV Antibiotics: ❑0 ❑1 ❑2 ❑3

Oral Cephalexin (Keflex)? ❑Yes ❑No

If Yes, Dose (mg): ❑250 ❑500 ❑1000

Oral Amoxicillin-Clavulanate? ❑Yes ❑No

If Yes, Dose (mg): ❑500 ❑875

Oral Amoxicillin? ❑Yes ❑No

If Yes, Dose (mg): ❑250 ❑500 ❑1000

Oral Clindamycin? ❑Yes ❑No

If Yes, Dose (mg): ❑300 ❑450 ❑600

Oral TMP-SMX (Septra)? ❑Yes ❑No

If Yes, Dose (mg): ❑800 (1 DS tab) ❑1600 (2 DS tabs)

Oral Ciprofloxacin? ❑Yes ❑No

If Yes, Dose (mg): ❑250 ❑500 ❑1000

IV Cefazolin (Ancef)? ❑Yes ❑No

If Yes, Dose (mg): ❑500 ❑1000 ❑1500 ❑2000

IV Ceftriaxone? ❑Yes ❑No

If Yes, Dose (mg): ❑1000 ❑1500 ❑2000

IV Clindamycin? ❑Yes ❑No

If Yes, Dose (mg): ❑300 ❑450 ❑600 ❑900

IV Meropenem? ❑Yes ❑No

If Yes, Dose (mg): ❑500 ❑1000 ❑1500 ❑2000

IV Vancomycin? ❑Yes ❑No

If Yes, Dose (mg): ❑500 ❑1000 ❑1500 ❑2000

IV Piperacillin-Tazobactam? ❑Yes ❑No

If Yes, Dose (mg): ❑3375 ❑4500

IV Ciprofloxacin? ❑Yes ❑No

If Yes, Dose (mg): ❑200 ❑400

ED Prescription:

Oral Cephalexin (Keflex)? ❑Yes ❑No
If Yes, Dose (mg): ❑250 ❑500 ❑1000
Frequency: ❑BID ❑TID ❑QID
Duration (days): _____

Oral Amoxicillin-Clavulanate? ❑Yes ❑No
If Yes, Dose (mg): ❑500 ❑875
Frequency: ❑BID ❑TID ❑QID
Duration (days): _____

Oral Amoxicillin? ❑Yes ❑No
If Yes, Dose (mg): ❑250 ❑500 ❑1000
Frequency: ❑BID ❑TID ❑QID
Duration (days): _____

Oral Clindamycin? ❑Yes ❑No
If Yes, Dose (mg): ❑300 ❑450 ❑600
Frequency: ❑BID ❑TID ❑QID
Duration (days): _____

Oral TMP-SMX (Septra)? ❑Yes ❑No
If Yes, Dose (mg): ❑800 (1 DS tab) ❑1600 (2 DS tabs)
Frequency: ❑OD ❑BID ❑TID
Duration (days): _____

Oral Ciprofloxacin? ❑Yes ❑No
If Yes, Dose (mg): ❑250 ❑500 ❑1000
Frequency: ❑OD ❑BID ❑TID
Duration (days): _____

Oral Doxycycline? ❑Yes ❑No
If Yes, Dose (mg): ❑100 ❑200
Frequency: ❑OD ❑BID ❑TID
Duration (days): _____

IV Cefazolin (Ancef)? ❑Yes ❑No
If Yes, Dose (mg): ❑500 ❑1000 ❑1500 ❑2000
Frequency: ❑BID ❑TID ❑QID
Duration (days): _____

IV Ceftriaxone? ❑Yes ❑No
If Yes, Dose (mg): ❑1000 ❑1500 ❑2000
Frequency: ❑OD ❑BID
Duration (days): _____

IV Clindamycin? ❑Yes ❑No
If Yes, Dose (mg): ❑300 ❑450 ❑600 ❑900
Frequency: ❑BID ❑TID ❑QID
Duration (days): _____

IV Meropenem? ❑Yes ❑No
If Yes, Dose (mg): ❑500 ❑1000 ❑1500 ❑2000
Frequency: ❑BID ❑TID ❑QID
Duration (days): _____

IV Vancomycin? ❑Yes ❑No
If Yes, Dose (mg): ❑500 ❑1000 ❑1500 ❑2000
Frequency: ❑OD ❑BID ❑TID
Duration (days): _____

IV Piperacillin-Tazobactam? ❑Yes ❑No
If Yes, Dose (mg): ❑3375 ❑4500
Frequency: ❑BID ❑TID ❑QID
Duration (days): _____

IV Ciprofloxacin? ❑Yes ❑No
If Yes, Dose (mg): ❑200 ❑400
Frequency: ❑BID ❑TID ❑QID
Duration (days): _____

Return to ED (RTED) within 14 days: ☐Yes ☐No

If yes (choose ONE only):

☐ Return to ED for SSTI and hospital admission

☐ Return to ED for SSTI but no admission

☐ Return to ED with abscess (If yes, I&D performed? ☐Yes ☐No)

☐Return to ED for repeat antibiotics: number of subsequent visits _____

☐ Return to ED for unrelated medical problem

If RTED: Changes to treatment in ED at repeat visit: ☐Yes ☐No

If yes (choose ONE only):

☐ Change from PO to IV antibiotics (name of new antibiotic:_____)

☐ Change to different PO antibiotic (name of new antibiotic:_____)

☐ Change to different IV antibiotic (name of new antibiotic:_____)

☐ Change to different antibiotic dose (new dose: ___ ___ ___ ___ mg)

If treatment was altered, reason for change in treatment plan:

☐ Worsening infection ☐ No improvement

☐ Vomiting ☐ Diarrhea ☐ Rash/hives

☐ Other Indicate: _____

<u>Oral Antibiotic Treatment Failure?</u> ❑Yes ❑No

If yes, reason for treatment failure (check all that apply):

❑ Step-up from PO to IV antibiotic

❑ Change in class of PO antibiotic (due to worsening infection)

❑ Initial outpatient management with subsequent hospital admission

<u>OPAT Treatment Failure?</u> ❑Yes ❑No

If yes (i.e. hospitalized from 48 hours – 2 weeks), reason for treatment failure (check all that apply):

❑ Worsening infection

❑ Drug-related complication

❑ Line-related complication

Adverse Events:

Adverse drug reaction: ❑Yes ❑No

If yes: ❑Rash

❑ Nausea only (no vomiting)

❑ Vomiting

❑ Diarrhea

❑ Other: _____

Adverse device event: ❑Yes ❑No

If yes: ❑Blocked peripheral IV

❑Dislodged peripheral IV

❑Line thrombosis

❑Line infection

Subsequent hospital admission at 14 days from index ED visit? ❑Yes ❑No

If yes: ❑For worsening SSTI

❑For unrelated medical problem (specify:_____)

OPAT Clinic:
Did patient attend OPAT appointment? ❑Yes ❑No (STOP HERE)
Cellulitis was correct diagnosis: ❑Yes ❑No
If NO – specify alternate diagnosis:
❑DVT ❑Lymphedema ❑Stasis dermatitis
❑Abscess ❑Hematoma ❑Drug rash

Number of days from initial ED visit to first OPAT appointment: _____

Total number of visits to OPAT clinic: _____

Total number of days on IV antibiotics: _____
Total number of days on IV and PO antibiotics: _____
IV Antibiotics for >7d? ❑Yes ❑No
IV Antibiotics for >10d? ❑Yes ❑No
Time to step-down (days) from IV to PO antibiotics: _____

<u>Rationale for IV antibiotics (check all that apply)</u>:

❑ Failed oral antibiotic therapy

❑ Hypotension

❑ Severe pain (>8/10)

❑ Clinical impression (severe infection)

❑ Diabetes

❑ Pain out of proportion

❑ Peripheral vascular disease

❑ Indwelling IV catheter

❑Bite

❑Social/compliance issues

❑Other: _____

Patient agreed to telephone call? ☐Yes ☐No ☐ Lost to follow-up
Patient expected to be referred to an outpatient clinic for management of infection?
☐Yes ☐No

Setting patient would prefer for receiving follow-up in the future?
☐ OPAT clinic ☐ ED ☐ Family doctor

Satisfaction with the timeliness of the referral to the OPAT clinic. _____/10

Overall satisfaction with care in the OPAT clinic: _____/10

Table S1. Reasons for Hospitalization within 14 Days of ED Visit for 137 Patients who attended their OPAT Clinic Appointment

Reason for Hospitalization	**Number of patients, N (%) N = 137**
Worsening infection	6 (4.4)
Other medical problem	4 (2.9)
Acute coronary syndrome	1
Renal failure	1
Gout	1
Hip fracture	1

Chapter Five: Discussion

Introduction

The goal of this thesis was to describe the epidemiology of adults with non-purulent SSTIs who present to the ED. Additional goals were to: (a) identify predictors associated with oral antibiotic treatment failure; (b) determine emergency physician rationale for selecting intravenous therapy; and (c) describe the performance of an ED-to-OPAT clinic program. This chapter will summarize the results of the health records review (Chapter Three) and the prospective observational cohort study (Chapter Four) in order to highlight clinical recommendations and areas for future research.

Interpretation of Results

The health records review (Chapter Three) described the epidemiology of adults with non-purulent SSTIs seeking care in the ED. There was a surprisingly high hospital admission rate, which in part reflects the need for more robust evidence-based guidelines to improve management of this common clinical condition. Many patients had diabetes and cellulitis within the preceding 12 months. We did observe a large variation in selection of the antimicrobial agent and route. The majority of patients received at least one dose of intravenous antibiotic in the ED. Despite a lack of evidence to support this practice, many patients received a single intravenous dose and were sent home with an oral antibiotic prescription. The observed variability in treatment approach highlights a clear lack of agreement amongst emergency physicians regarding optimal antimicrobial therapy for this common

clinical condition. Due to the study design, the reasons behind selecting intravenous therapy remained unclear.

We found an oral antibiotic treatment failure rate that was higher than expected in the health records review when compared to prior studies.[1,2] These prior studies did not use a strict time cutoff to define treatment failure, which may have led to some patients being misclassified as treatment failure or success. We used multivariable logistic regression to identify factors associated with oral antibiotic treatment failure. A detailed description of the methods used to develop a multivariable logistic regression model can be found in Appendix B. We first used clinical reasoning to determine which variables could plausibly predict oral antibiotic treatment failure. Ultimately, seven variables were chosen for inclusion into a multivariable model. Four variables were found to be associated with the primary outcome: tachypnea at triage; chronic ulcers; a history of MRSA colonization or infection; and prior cellulitis in the last 12 months. This is the first study to identify potential predictors associated with oral antibiotic treatment failure.

To address the issues we identified surrounding intravenous antibiotic use, we conducted a prospective observational cohort study (Chapter Four) to: (a) describe the performance of an ED-to-OPAT clinic model; and (b) identify physician rationale for selecting intravenous therapy. We found low rates of OPAT treatment failure. None of the adverse peripheral intravenous line events or adverse antibiotic events

was serious enough to require hospitalization. The diagnosis of non-purulent SSTIs was concordant between emergency physicians and infectious disease specialists in the majority of cases. Patients reported a high degree of satisfaction with timeliness of referral and overall care received. Our findings suggest that an ED-to-OPAT clinic model is safe and acceptable to patients.

There was significant emergency physician practice variation in the prospective observational cohort study. The most commonly prescribed intravenous antibiotic was cefazolin; physicians were almost evenly split regarding the chosen dose. The top five reasons for selecting the intravenous route were: clinical impression; failed oral antibiotic therapy; diabetes; severe pain; and peripheral vascular disease. Oral antibiotic failure was the second most common reason for selecting the parenteral route, which is interesting given the lack of a validated definition of treatment failure. The presence of comorbidities (diabetes and peripheral vascular disease) as rationale for intravenous therapy was noteworthy given that neither was found to be associated with oral antibiotic failure in the health records review.

Previous Studies

The 2014 Infectious Disease Society of America guidelines are largely based on expert opinion, and suggest intravenous antibiotics for 'moderate' (signs of systemic illness) or 'severe' (failed oral therapy, signs of systemic illness, clinical signs of deeper infection, or immunocompromised) infections.[3] The British Clinical Resource Efficiency Support Team (CREST) guidelines recommend oral antibiotics in 'Class I'

patients, which is defined as a lack of systemic signs of illness and the absence of 'uncontrolled comorbidities'.[4] The latter was not explicitly defined. There are currently no Canadian guidelines for this important topic. Peterson and coworkers identified predictors of treatment failure with outpatient antibiotic therapy, but did not distinguish between oral versus intravenous routes.[2] Despite the lack of evidence, a recent national survey of Canadian emergency physicians found that 94.4% of respondents would consider a clinical decision rule to predict oral antibiotic treatment failure.[5]

The observed low OPAT treatment failure rate in the prospective observational cohort study was similar to previously published studies.[6-8] Current guidelines list patient satisfaction as a critical element of an OPAT program.[9-11] We found a high degree of patient satisfaction that is similar to previous studies. An additional aim of our study was to answer the clinical question: *why do emergency physicians select the intravenous route for antimicrobial therapy?* We felt that this was an important clinical question, as appropriate patient selection for outpatient intravenous therapy is a critical first step to the success of an OPAT program.[9,12] There are no previously published prospective studies that have examined physician rationale for selecting the intravenous route.

Strengths

The health records review is the first study to identify potential predictors associated with oral antibiotic treatment failure for non-purulent SSTIs. We used strict inclusion and exclusion criteria, predefined variables, a standardized case record form, and held regular meetings between data abstractors to resolve outstanding issues and to perform appropriate oversight. These specific steps were taken in order to minimize bias, in accordance with accepted methodology for chart reviews.[13-16] There was excellent agreement among data abstractors for both study inclusion and the primary outcome.

For the prospective observational cohort study, we enrolled a consecutive sample of patients and screened all OPAT clinic referrals to ensure no eligible cases were missed. The data were collected prospectively, which allowed us to accurately identify emergency physician rationale for selecting the intravenous route. This is the first study to provide important insight into physician decision-making regarding selection of intravenous antibiotic therapy.

Limitations

The health records review has several potential limitations. First, we felt that the size of an infection (area of erythema) could be a clinically important marker of infection severity. However, we suspected that most emergency physicians might not accurately document infection size or omit this information. In order to mitigate this problem for the health records review, we developed an a priori method to estimate infection size using total body surface area extrapolated from a Lund-

Browder burn diagram.[17,18] Given the limitations of the study design, this provided the best estimate of infection size. Second, obesity as a comorbidity may have not been consistently documented in the chart. To address this issue, we reviewed electronic health records in the six months prior to and after the index ED visit to determine if obesity was documented elsewhere.

Third, the data abstractors were not blinded to the primary outcome of oral antibiotic treatment failure. However, we used a definition of oral antibiotic treatment failure that incorporated a clear minimum of 48 hours of oral therapy before a patient could be considered a possible treatment failure. There was also excellent interobserver agreement for the primary outcome. Therefore, we feel the lack of blinding of the study abstractors would not have introduced significant bias.

A fourth potential limitation of the health records review was over fitting of data due to the number of variables considered as possible predictors of oral antibiotic treatment failure. We initially investigated 18 variables using univariate analysis and identified seven variables that were associated with the primary outcome. These seven variables were then entered into a multivariable model. However, this was a health records review intended to help identify potential predictors. Based on the results of the health records review, we intend to assess a smaller number of variables in a future prospective cohort study.

A limitation of both studies (health records review and prospective observational cohort study) is the lack of a validated definition for oral or intravenous antibiotic treatment failure. We first reviewed the literature[1,2,5,19-24] and then developed treatment failure definitions after discussion among local experts in emergency medicine and infectious disease.

For the prospective observational cohort study, there are additional limitations that deserve mention. First, the sample size was limited due to feasibility. Second, some patients did not attend their clinic appointment. It is possible that some of these patients lost to follow-up experienced a treatment failure and sought care at another hospital. However, we feel it would be unlikely for patients to visit a hospital different from the centre that initiated their care for an infection. Third, it was not feasible to accurately weigh patients to determine body mass index and degree of obesity. While it is possible that the observed variation in antibiotic dosing may be in part due to patient body habitus, this would be a minor issue as only a small percentage of patients were recorded as obese in this study cohort.

Clinical Implications

The results from the health records review highlight important clinical implications given the practice variation with respect to antibiotic agent, dose, frequency and route. In addition, we found an unexpectedly high hospital admission rate and oral antibiotic treatment failure rate. These findings are likely due to a lack of evidence-based recommendations to guide clinicians on optimal treatment of this common

clinical condition. We identified risk factors associated with oral antibiotic treatment failure. These factors should be considered by emergency physicians when deciding on the oral versus intravenous route of antibiotic therapy; this may in turn decrease overuse of more invasive and costly intravenous treatment.

The prospective observational cohort study also identified a lack of consensus regarding antibiotic prescribing practices among emergency physicians. It is the first study to identify emergency physician rationale for selecting intravenous therapy for non-purulent SSTIs. This is an important first step to better understand physician decision-making when selecting the intravenous route. The rate of OPAT treatment failure was low, and none of the adverse antibiotic events or adverse peripheral intravenous line events required hospitalization. An ED-to-OPAT clinic model was found to be effective, safe and results in a high degree of patient satisfaction. This model may be introduced in other communities to potentially reduce hospital admissions and overall healthcare costs.

To summarize, based on the two studies conducted, we can make the following clinical recommendations:

1. Emergency physicians should consider certain factors (tachypnea, chronic leg ulcers, a history of MRSA colonization or infection, and prior cellulitis in the past 12 months) when deciding on intravenous (over oral) antibiotic therapy for non-purulent SSTIs.

2. An ED-to-OPAT clinic model is safe and results in a high degree of patient satisfaction. This model may be implemented in other communities to help reduce hospital admissions and overall healthcare costs.

Research Implications

The findings from this thesis project have highlighted important issues that we aim to address in future studies:

1. Develop and validate a robust definition for oral and intravenous antibiotic treatment failure using the Delphi method. These definitions may be used in future studies on this topic.
2. Conduct a prospective observational cohort study to derive a model to identify factors associated with oral antibiotic treatment failure. We will select a fewer number of potential predictor variables a priori based on the results of this thesis project. This model will then be validated in a separate ED population.
3. Design and implement a pilot randomized controlled trial comparing oral versus intravenous antibiotics in the treatment of adult patients with non-purulent SSTIs.

Prior ED-based studies have used different treatment failure definitions as the primary outcome.[1,2,22] Future studies would be more impactful by incorporating a uniform and robust treatment failure definition. We plan to use the Delphi method to develop and validate definitions of oral and intravenous antibiotic treatment

failure. The Delphi method is a systematic approach that has been used to develop clinical definitions[25] and guidelines[26] based on expert opinion. Consensus will be defined a priori as ≥75%, which is the most common threshold used in prior Delphi studies.[27] Relevant stakeholders will include emergency physicians, infectious specialists, pharmacists and patients. The Delphi process will be conducted in sequential rounds until consensus has been achieved. Structured definitions for oral and intravenous antibiotic treatment failure for SSTIs may be utilized in future studies.

Chapter Three identified possible predictors associated with oral antibiotic treatment failure. We plan to conduct a prospective observational cohort study to identify predictors associated with oral antibiotic treatment failure. The research team will record infection size and body mass index (measure of obesity) for eligible patients, and both variables will be assessed as potential predictors of treatment failure. In Chapter Four, several physician rationales for selecting the intravenous route were identified, including diabetes and peripheral vascular disease. For our planned prospective cohort study, a fewer number of predictor variables will be selected based on the results of the health records review (Chapter Three), prospective observational cohort study (Chapter Four) and expert opinion from emergency physician and infectious disease specialists. For the primary outcome, we will use the definition of oral antibiotic treatment failure developed from our planned Delphi study. This study will more accurately identify which factors predict oral antibiotic treatment failure, and may help emergency physicians decide which

patients require intravenous versus oral antimicrobial therapy. This may help limit overuse of intravenous antibiotics and lower rates of adverse events and overall healthcare costs.

Ultimately, we aim to conduct a future randomized controlled trial comparing oral versus intravenous antibiotic therapy for non-purulent SSTIs. Before conducting such a large-scale study, we intend to design and implement a pilot randomized control trial to assess feasibility. Eligible adult ED patients with non-purulent SSTIs would be randomized to receive either oral cephalexin or intravenous cefazolin, and the primary outcome would be oral or intravenous antibiotic treatment failure.

Conclusions

This thesis project has accomplished specific goals regarding non-purulent SSTIs that are managed in the ED. Our first study (health records review) describes the management of all patients with non-purulent SSTIs presenting to the ED. The study findings highlight the heterogeneity in antimicrobial treatment route and agent. Furthermore, we observed both an unexpectedly high hospital admission rate and oral antibiotic treatment failure rate. Ultimately, we were able to develop a multivariable logistic regression model of factors associated with oral antibiotic treatment failure. Our second study (prospective observational cohort study) showed that an ED-to-OPAT clinic model is both safe and results in high patient satisfaction. We also identified physician rationales for selecting the intravenous route.

The results have highlighted key areas in which future studies are required to better inform emergency physicians regarding: (a) optimal therapy of this common clinical condition; and (b) appropriate patient selection for outpatient intravenous therapy. Both the identified factors associated with oral antibiotic failure and emergency physician rationales for intravenous therapy deserve future study. More robust evidence regarding which factors truly predict oral antibiotic failure would help emergency physicians more appropriately select patients for intravenous therapy and reduce the incidence of treatment failure. We are optimistic that this will in turn result in better patient care, an important improvement in the appropriate use of intravenous antibiotic therapy, and a reduction in healthcare costs.

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Appendix A: Ottawa Health Science Network Research Ethics Board Approval Letter

Ottawa Hospital Research Institute
Institut de recherche de l'Hôpital d'Ottawa

uOttawa

UNIVERSITY OF OTT
HEART INSTITU
INSTITUT DE CARDIOL
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Ottawa Health Science Network Research Ethics Board/ Conseil d'éthique de la recherche
Réseau de science de la santé d'Ottawa

[redacted]

http://www.ohri.ca/ohsn-reb

December 21, 2016

[redacted]

Dear Dr. [redacted]

Re: Protocol # 20160509-01H Non-Purulent Skin and Soft Tissue Infections in the Emerg Department

Thank you for the submission that was received in our offices November 28, 2016.

The Protocol Amendement Report dated November 23, 2016 is approved. The following are alsc approved:
-Revised Protocol dated November 25, 2016.
-Revised CRF dated November 25, 2016.

Ethical approval remains in effect until November 20, 2017.

OHSN-REB complies with the membership requirements and operates in compliance with the Tr Council Policy Statement: Ethical Conduct for Research Involving Humans; the International Conference on Harmonization - Good Clinical Practice: Consolidated Guideline; and the provisio the Personal Health Information Protection Act 2004.

Yours sincerely,

[redacted]

Vice-Chairperson
Ottawa Health Science Network Research Ethics Board

Appendix B: Methods for Developing a Multivariable Logistic Regression Model for Predictors of Oral Antibiotic Treatment Failure

Introduction

We conducted a health records review of 500 adult emergency department (ED) patients with non-purulent skin and soft tissue infections (SSTIs). Our aim was to identify predictors associated with the primary outcome of oral antibiotic treatment failure. Of the total cohort of 500 patients, 288 patients were treated with oral antibiotics and 85 patients experienced an oral antibiotic treatment failure.

Exploratory Analysis

Table B1 summarizes the characteristics of the 288 patients treated with oral antibiotics based on whether or not they experienced a treatment failure. For continuous variables, we plotted histograms to assess the distribution of the variables. Age, systolic blood pressure, heart rate and temperature were approximately normally distributed. Respiratory rate, oxygen saturation, white blood cell count and area of erythema were non-normally distributed. Comparing the patients who did and did not experience an oral antibiotic treatment failure, categorical variables were assessed using the chi-square or Fisher's exact test, and continuous variables were assessed using t-tests for normally distributed variables and Wilcoxon tests for non-normally distributed variables.

Outliers

There was a single outlier for each of the following variables: white blood cell count (75×10^9/L), respiratory rate (40 breaths/minute) and oxygen saturation (82%). The patient with a high white blood cell count had leukemia. None of these outliers are physiologically impossible, and so these were not removed.

Missing Data

The variable area of erythema was missing in 88.2% of cases. Because we felt that infection size may be a potentially important predictor for the primary outcome, we estimated the percent total body surface area for all cases using a Lund-Browder burn diagram.[1,2] White blood cell count was missing in 24.4% of cases. All remaining continuous variables had less than 4% missing data.

Excluding Variables

The variable area of erythema was excluded because of a significant proportion of missing data. The variables white blood cell count and oxygen saturation were excluded because we determined it did not make clinical sense that either variable would be associated with treatment failure. Four variables had a sparse distribution (i.e. low frequency (<1%) cells on crosstabs of the variables by oral antibiotic treatment failure): bite, HIV, injection drug use and organ transplant recipient; we removed these variables for consideration as potential predictors in our model. Thus we were left with 18 variables (5 continuous, 13 categorical) that we felt could plausibly be associated with oral antibiotic treatment failure.

Table B1. Univariate Association of Characteristics with Treatment Failure of the Study Participants (N=288)

Variable (N)	Oral Treatment Failure Frequency, n (%) (N = 85)	No Oral Treatment Failure Frequency, n (%) (N = 203)	P Value*
Male (158)	48 (56.5)	110 (54.2)	0.72
Chronic ulcers (20)	13 (15.3)	7 (3.4)	0.0003
Surgical site infection (20)	7 (8.2)	13 (6.4)	0.58
Bite (8)	1 (1.2)	7 (3.4)	0.44
>5% TBSA (39)	14 (16.5)	25 (12.3)	0.35
Coronary artery disease (29)	12 (14.1)	17 (8.4)	0.14
Congestive heart failure (18)	8 (9.4)	10 (4.9)	0.15
Chronic kidney disease (15)	8 (9.4)	7 (3.4)	0.04
Chronic venous insufficiency (8)	1 (1.2)	7 (3.4)	0.44
Diabetes mellitus (55)	23 (27.1)	32 (15.8)	0.03
Liver disease (17)	5 (5.9)	5 (5.9)	0.99
HIV (2)	2 (2.4)	0 (0)	0.09
Injection drug use (IVDU) (4)	3 (3.5)	1 (0.5)	0.08
Lymphedema (14)	5 (5.9)	9 (4.4)	0.56
History of MRSA colonization or infection (16)	11 (12.9)	5 (2.5)	0.001
Obesity (8)	3 (3.5)	5 (2.5)	0.69
Prior cellulitis in past 12 months (38)	19 (22.4)	19 (9.4)	0.003
Peripheral vascular disease (17)	5 (5.9)	12 (5.9)	0.99
Age (mean ± SD)	67.1 ± 19.0	63.3 ± 20.3	0.15
Systolic blood pressure (mean ± SD)	140 ± 22	138 ± 24	0.69
Heart rate (mean ± SD)	84 ± 17	83 ± 16	0.68
Temperature (mean ± SD)	36.6 ± 0.8	36.3 ± 0.7	0.01
Respiratory rate (median, IQR)	18 (16 – 18)	16 (16 – 18)	0.85
SaO_2 (median, IQR)	97 (96 – 98)	97 (96 – 98)	0.11
WBC count (median, IQR)	8.6 (7.0 – 12.1)	8.2 (6.4 – 11.1)	0.21

TBSA = total body surface area; HIV = human immunodeficiency virus; SaO_2 = oxygen saturation; WBC = white blood cell; SD = standard deviation; IQR = interquartile range (Q1 – Q3)

Associations between categorical variables

We considered several categorical variables where it was clinically plausible that they may be collinear. Table B2 shows the degree of collinearity between the categorical variables using the Phi coefficient.[3]

Table B2. Assessment of Simple Collinearity Between Categorical Variables Using the Phi Coefficient

	Gender	Chronic Ulcers	% TBSA	DM	Lymphedema	MRSA	Obesity	Prior SSTI	PVD
Gender		0.05	-0.02	0.07	-0.13	0.0001	0.03	0.005	-0.005
Chronic Ulcers	0.05		0.05	0.13	0.08	0.12	0.08	0.17	0.24
%TBSA	-0.02	0.05							
DM	-0.07	0.13	0.16		0.05	0.12	0.15	0.12	0.22
Lymphedema	-0.13	0.08	0.17	0.05		0.005	0.15	0.11	0.01
MRSA	0.0001	0.12	0.04	0.12	0.005		0.05	0.16	-0.01
Obesity	0.03	0.08	-0.008	0.15	0.15	0.05		0.15	-0.005
Prior SSTI	0.005	0.17	0.12	0.12	0.11	0.16	0.15		-0.02
PVD	-0.005	0.24	0.11	0.22	0.01	-0.01	-0.005	-0.02	

DM = diabetes mellitus; TBSA = total body surface area; MRSA = prior methicillin resistant *Staphylococcus aureus* (MRSA) colonization or infection; Prior SSTI = cellulitis within the past 12 months; PVD = peripheral vascular disease

Interpretation of the Phi coefficient was as follows: strong positive association (0.7 to 1.0); weak positive association (0.3 to 0.7); little or no association (-0.3 to 0.3); weak negative association (-0.7 to -0.3); and strong negative association (-1.0 to -0.7). There were no strong positive or negative associations. Because there was no high degree of collinearity, we did not need to consider exclusion of any of the categorical variables in Table B2.

Correlation between continuous variables

In Table B3 the correlation between continuous variables using the Pearson correlation coefficient (r) are provided. The same ranges for the Phi coefficient were

used to interpret the Pearson correlation coefficients. There were no strong positive or negative linear associations between the continuous variables, as none of the Pearson correlation coefficients approached +1 or -1.

Table B3. Correlation Between Continuous Variables Using Pearson Correlation Coefficient (r)

Pearson r coefficient	Age	SBP	HR	Temp	RR	SaO_2
Age	1	0.12	-0.23	-0.001	0.07	-0.24
SBP	0.12	1	-0.07	-0.05	-0.04	-0.01
HR	-0.23	-0.07	1	0.25	0.20	0.03
Temp	-0.008	-0.05	0.25	1	0.28	-0.08
RR	0.07	-0.04	0.19	0.28	1	-0.08
SaO_2	-0.24	-0.01	0.03	-0.08	-0.09	1

SBP = systolic blood pressure; HR = heart rate; Temp = temperature; RR = respiratory rate; SaO_2 = oxygen saturation

Logistic Regression Analysis

Univariate Analysis

Following the exploratory analysis, there were 18 variables (5 continuous and 13 categorical) that we felt merited consideration as potential predictors based on clinical sensibility.

For the 5 continuous variables, we considered clinically meaningful cutoffs and performed univariate logistic regression. In addition, we did explore a range of cutoffs to determine if there were any trends. We determined age ≥ 65 years to be the most clinically relevant, which is the definition employed by the most recent geriatric ED guidelines.[4] For the triage vital signs, the following cutoffs were selected: systolic blood pressure <90mmHg (clinically relevant hypotension); heart

rate ≥ 100 beats per minute (clinical definition of tachycardia); respiratory rate > 20 breaths per minute (clinical definition of tachypnea); and temperature ≥ 38.0°C (clinical definition of fever). The univariate logistic regression analysis of the continuous variables at prespecified cutoffs are summarized in Tables B4 – B8. These cutoffs were selected based on standard definitions and clinical reasoning and are shown with various other cutoffs to show any potential trends.

Table B4. Univariate Logistic Regression for Age as a Predictor of Oral Antibiotic Treatment Failure

Predictor Variable	Estimate	P Value	OR	95% CI
Age ≥ 50	0.40	0.21	1.49	0.80 – 2.75
Age ≥ 55	0.38	0.20	1.46	0.82 – 2.62
Age ≥ 60	0.35	0.21	1.42	0.82 – 2.43
Age ≥ 65*	0.21	0.42	1.24	0.74 – 2.06
Age ≥ 70	0.02	0.95	1.01	0.61 – 1.69
Age ≥ 75	0.15	0.57	1.16	0.69 – 1.95
Age ≥ 80	0.22	0.44	1.25	0.71 – 2.18
Age ≥ 85	0.25	0.44	1.29	0.67 – 2.46

*Selected as the most clinically relevant cutoff
OR = odds ratio; CI = confidence interval

Table B5. Univariate Logistic Regression for Systolic Blood Pressure as a Predictor of Oral Antibiotic Treatment Failure

Predictor Variable	Estimate	P Value	OR	95% CI
SBP <85	0.90	0.53	2.45	0.15 – 39.64
SBP <90*	0.90	0.52	2.45	0.15 – 39.64
SBP <100	0.04	0.95	1.04	0.26 – 4.14
SBP < 110	-0.36	0.49	0.70	0.25 – 1.96

*Selected as the most clinically relevant cutoff
SBP = systolic blood pressure; OR = odds ratio; CI = confidence interval

Table B6. Univariate Logistic Regression for Heart Rate as a Predictor of Oral Antibiotic Treatment Failure

Predictor Variable	Estimate	P Value	OR	95% CI
HR ≥ 90	-0.14	0.61	0.87	0.50 – 1.50
HR ≥ 100*	0.33	0.35	1.39	0.70 – 2.77
HR ≥ 110	0.59	0.22	1.80	0.70 – 4.66
HR ≥ 120	0.90	0.16	2.46	0.69 – 8.74

*Selected as the most clinically relevant cutoff
HR = heart rate; OR = odds ratio; CI = confidence interval

Table B7. Univariate Logistic Regression for Temperature as a Predictor of Oral Antibiotic Treatment Failure

Predictor Variable	Estimate	P Value	OR	95% CI
T ≥ 38.0*	1.14	**0.09**	3.13	0.82 – 11.98
T ≥ 38.5	2.01	0.08	7.44	0.76 – 72.6

*Selected as the most clinically relevant cutoff
T = temperature; OR = odds ratio; CI = confidence interval

Table B8. Univariate Logistic Regression for Respiratory Rate as a Predictor of Oral Antibiotic Treatment Failure

Predictor Variable	Estimate	P Value	OR	95% CI
RR ≥ 20	0.14	0.70	1.15	0.57 – 2.30
RR > 20*	1.78	**0.004**	5.95	1.78 – 19.91
RR ≥ 22	1.78	0.004	5.95	1.78 – 19.91
RR ≥ 24	3.05	0.004	21.19	2.60 – 172.3

*Selected as the most clinically relevant cutoff
RR = respiratory rate; OR = odds ratio; CI = confidence interval

At our chosen cutoff of 65 years, age was not associated with oral antibiotic treatment failure. The same was true for a variety of other cutoffs as shown in Table 4. Hypotension and tachycardia were also not associated with the primary outcome (Tables B5 and B6). However, fever and tachypnea were associated with the

primary outcome (Tables B7 and B8), and these variables were selected for the multivariable model.

Table B9 shows the univariate logistic regression for 13 categorical variables. We found five variables that were associated with the primary outcome (p-value ≤0.10): chronic ulcers; chronic kidney disease; diabetes mellitus; a history of MRSA colonization or infection; and prior cellulitis in the past 12 months.

Table B9. Simple Univariate Logistic Regression for Categorical Variables

Predictor Variable	Estimate	P Value	OR	95% CI
Male	0.09	0.72	1.10	0.66 – 1.83
Chronic Ulcers	1.62	**0.0009**	5.06	1.94 – 13.17
Surgical site infection	0.27	0.58	1.31	0.50 – 3.41
TBSA >5%	0.34	0.35	1.40	0.69 – 2.86
Coronary artery disease	0.59	0.14	1.80	0.82 – 3.95
Congestive heart failure	0.70	0.16	2.01	0.76 – 5.27
Chronic kidney disease	1.07	**0.04**	2.91	1.02 – 8.30
Diabetes mellitus	0.68	**0.03**	1.98	1.08 – 3.65
Lymphedema	0.30	0.60	1.35	0.44 – 4.14
History of MRSA colonization or infection	1.77	**0.001**	5.89	1.98 – 17.51
Obesity	0.37	0.62	1.45	0.34 – 6.20
Prior cellulitis in last 12 months	1.02	**0.004**	2.79	1.39 – 5.59
Peripheral vascular disease	-0.005	0.99	0.99	0.34 – 2.92

TBSA = total body surface area; MRSA = methicillin resistant *Staphylococcus aureus*; OR = odds ratio; CI = confidence interval

In summary, following an exploratory analysis and univariate logistic regression analysis, we identified seven variables with a p-value ≤0.10 that we chose to include in a multivariable logistic regression model:

1. Fever (temperature ≥ 38.0°C)
2. Tachypnea (respiratory rate > 20 breaths/minute)
3. Chronic ulcers
4. Chronic kidney disease
5. Diabetes mellitus
6. Past MRSA colonization or infection
7. Prior cellulitis in the past 12 months

Given that there were 85 identified cases of oral antibiotic treatment failure, testing 7 variables would satisfy the rule of 10.[5-7]

Assessing for Interaction

Where it seemed clinically plausible, we assessed for possible interaction between the seven potential predictor variables. Investigation for potential interaction terms is summarized in Table B10. None of the interaction terms was significant (defined as p≤0.05), and so no interaction terms were brought into a multivariable model.

Table B10. Assessment of Possible Interaction Terms

Predictor Variable	Estimate	P Value
Diabetes*CKD	-0.26	0.82
Chronic Ulcers*Diabetes	13.60	0.99
Chronic Ulcers*PVD	1.32	0.37
Chronic Ulcers*Lymphedema	0.06	0.96
Prior cellulitis*MRSA history	0.36	0.79
Prior cellulitis*Lymphedema	-1.86	0.17
Prior cellulitis*PVD	15.13	0.99
Prior cellulitis*Diabetes	-1.57	0.08
Fever*Tachypnea	13.66	0.99

CKD = chronic kidney disease; PVD = peripheral vascular disease; MRSA = methicillin resistant *Staphylococcus aureus*; PVD = peripheral vascular disease

Multivariable Logistic Regression: Preliminary Model

We performed multivariable logistic regression including seven potential predictor variables with p≤0.10 in the univariate analysis. Table B11 shows the preliminary model.

Table B11. Multivariable Logistic Regression Model of Predictors Associated with Oral Antibiotic Treatment Failure (N=288)

Predictor Variable	Estimate	P Value	Adjusted OR	95% CI
Tachypnea (RR>20)	1.64	0.01	5.15	1.41 – 18.86
Chronic ulcers	1.57	0.004	4.80	1.64 – 14.04
History of MRSA colonization or infection	1.56	0.008	4.78	1.49 – 15.31
Prior cellulitis in last 12 months	0.76	0.06	2.14	0.96 – 4.74
Chronic kidney disease	1.08	0.08	2.94	0.89 – 9.70
Diabetes mellitus	0.53	0.13	1.70	0.86 – 3.63
Fever (T ≥ 38.0)	0.82	0.34	2.26	0.42 – 12.24
The Hosmer-Lemeshow chi-square test yielded a p-value of 0.938 (chi-squared = 0.409, degrees of freedom = 3). C-statistic = 0.710.				

RR = respiratory rate; MRSA = methicillin resistant *Staphylococcus* aureus; T = temperature; OR = odds ratio; CI = confidence interval

Table B12 shows the backwards selection logistic regression model including the same seven variables with an inclusion criteria set as a p-value ≤0.15. The backwards selection model dropped one variable (fever).

Table B12. Multivariable Logistic Regression Model Using Backwards Selection of Predictors of Oral Antibiotic Treatment Failure (N=288)

Predictor Variable	Estimate	P Value	Adjusted OR	95% CI
Tachypnea (RR> 20)	1.80	**0.005**	6.08	1.74 – 21.31
Chronic ulcers	1.56	**0.004**	4.74	1.63 – 13.84
History of MRSA colonization or infection	1.55	**0.009**	4.70	1.47 – 15.01
Chronic kidney disease	1.05	0.08	2.87	0.87 – 9.46
Prior cellulitis in past 12 months	0.78	0.06	2.17	0.98 – 4.82
Diabetes mellitus	0.55	0.11	1.74	0.88 – 3.43
The Hosmer-Lemeshow chi-square test yielded a p-value of 0.611 (chi-squared = 1.819, degrees of freedom = 3). C-statistic = 0.710.				

RR = respiratory rate; MRSA = methicillin resistant *Staphylococcus* aureus; T = temperature; OR = odds ratio; CI = confidence interval

As a final step, the remaining 6 variables from the backwards selection model were placed into a multivariable logistic regression model. The final model is shown in Table B13.

Table B13. Final Multivariable Logistic Regression Model of Predictors Associated with Oral Antibiotic Treatment Failure (N=288)

Predictor Variable	Estimate	P Value	Adjusted OR	95% CI
Tachypnea (RR>20)	1.84	0.004	6.31	1.80 – 22.08
Chronic ulcers	1.59	0.004	4.90	1.68 – 14.27
History of MRSA colonization or infection	1.58	0.008	4.83	1.51 – 15.44
Prior cellulitis in past 12 months	0.80	0.05	2.23	1.01 – 4.96
Chronic kidney disease	1.59	0.10	2.60	0.82 – 8.22
Diabetes mellitus	0.53	0.12	1.70	0.87 – 3.32
The Hosmer-Lemeshow chi-square test yielded a p-value of 0.604 (chi-squared = 1.853, degrees of freedom = 3). C-statistic = 0.709.				

The Hosmer-Lemeshow goodness of fit (p=0.604) indicates no evidence of poor fit and the C-statistic (0.709) suggest the model has good fit. The variables that

remained significant ($p \leq 0.05$) in the multivariable model were: tachypnea, chronic ulcers, history of MRSA colonization or infection, and prior cellulitis in the past 12 months. Since diabetics are prone to developing lower extremity ulcers[8-10], as a final step, we checked for possible interaction between diabetes mellitus and chronic ulcers. This yielded a p-value = 0.99, indicating no significant interaction between these variables.

Secondary Analysis (Comparing Oral vs. Intravenous Treatment Groups)

We conducted a secondary analysis comparing the oral antibiotic treatment group (N=288) and intravenous antibiotic treatment group (N=212). The results are summarized in Tables B14 and B15.

Table B14. Secondary Analysis Comparing Oral versus Intravenous Antibiotic Groups for Categorical Variables for all 500 Patients

Variable (n)	Oral Antibiotic Group Frequency, n (%) (n = 288)	IV Antibiotic Group Frequency, n (%) (n = 212)	P Value*
Male (279)	158 (54.9)	121 (57.1)	0.62
Chronic Ulcers (56)	20 (6.9)	36 (17.0)	0.0004
Surgical Site Infection (30)	20 (6.9)	10 (4.7)	0.30
Bite (12)	8 (2.8)	4 (1.9)	0.52
>5% TBSA (99)	39 (13.5)	60 (28.3)	<0.0001
Coronary artery disease (58)	29 (10.1)	29 (13.7)	0.21
Congestive heart failure (48)	18 (6.2)	30 (14.1)	0.003
Chronic kidney disease (35)	15 (5.2)	20 (9.4)	0.07
Chronic venous insufficiency (10)	8 (2.8)	2 (0.9)	0.20
Diabetes mellitus (126)	55 (19.1)	71 (33.5)	0.0002
Hepatic Disease (37)	17 (5.9)	20 (9.4)	0.14
HIV (8)	2 (0.7)	6 (2.8)	0.08
IVDU (14)	4 (1.4)	10 (4.7)	0.02
Lymphedema (33)	14 (4.9)	19 (9.0)	0.07
MRSA History (43)	16 (5.6)	27 (12.7)	0.005
Obesity (27)	8 (2.8)	19 (9.0)	0.002
Prior cellulitis (87)	38 (13.2)	49 (23.1)	0.004
PVD (40)	17 (5.9)	23 (10.8)	0.04

*Using Chi-Squared or Fisher's Exact Test

IV = intravenous; TBSA = total body surface area; HIV = human immunodeficiency virus; IVDU = intravenous drug use; MRSA = methicillin resistant *Staphylococcus aureus*; PVD = peripheral vascular disease

Table B15. Secondary Analysis Comparing Oral versus Intravenous Antibiotic Groups for Continuous Variables for all 500 Patients

Variable (n)	Oral Antibiotic Group Frequency, n (%) (N = 288)	IV Antibiotic Group Frequency, n (%) (N = 212)	P Value*
Age (mean ± SD)	64.4 ± 20.0	64.3 ± 16.9	0.95
Systolic BP (mean ± SD)	139 ± 23	131 ± 25	0.0007
Heart rate (mean ± SD)	84 ± 16	90 ± 21	<0.0001
Temperature (mean ± SD)	36.4 ± 0.8	36.8 ± 1.2	<0.0001
Respiratory Rate (median, IQR)	16 (16 – 18)	18 (16 – 20)	0.02
SaO_2 (median, IQR)	97 (96 – 98)	97 (96 – 98)	0.88
WBC count (median, IQR)	8.2 (6.6 – 11.2)	10.4 (7.7 – 14.7)	<0.0001

*Using t-tests for normally distributed variables, Wilcoxon tests for non-normally distributed variables
SD = standard deviation; IQR = interquartile range; IV = intravenous; BP = blood pressure; HR = heart rate; SaO_2 = oxygen saturation; WBC = white blood cell

Patients were more likely to receive intravenous antibiotics if they had chronic ulcers, large area of involvement (total body surface area >5%), congestive heart failure, diabetes, injection drug use, a history of MRSA colonization or infection, prior cellulitis in the past 12 months and peripheral vascular disease. Patients treated with intravenous antibiotics also had a higher median respiratory rate and higher mean systolic blood pressure, heart rate and temperature. These results suggest that emergency physicians appear to be more likely to administer intravenous antibiotics to patients with triage vital signs or comorbidities that were associated with treatment failure in the final model (Table B13).

Discussion

Our study identified potential risk factors associated with oral antibiotic treatment failure for adults presenting to the ED with non-purulent SSTIs. The number of

variables under consideration was reduced by eliminating variables with >20% missing data or with sparse distributions. We chose to only include variables where it was clinically plausible that they may be associated with the primary outcome. We did not identify a high degree of collinearity between variables. Following the exploratory analysis, univariate logistic regression identified seven variables associated with the primary outcome.

We then developed a final multivariable logistic regression model that included six variables. Four variables were independently associated with oral antibiotic treatment failure: tachypnea; chronic ulcers; a history of MRSA colonization or infection; and prior cellulitis in the past 12 months. The Hosmer-Lemeshow goodness-of-fit suggests no evidence of poor fit and the C-statistic indicates that the model has good fit. We also looked at possible interaction between independent variables but did not identify any significant interaction terms.

One important limitation to our approach was that the data might be over fitted. However, as this was a health records review, the purpose was to try and identify potential associations with oral antibiotic treatment failure. We plan to conduct future prospective studies incorporating fewer variables to develop a model.

Conclusion

To our knowledge, this is the first study to identify predictor variables independently associated with oral antibiotic treatment failure. Emergency

physicians should consider these risk factors when selecting the appropriate route of antimicrobial therapy for a patient with a non-purulent SSTI. Future prospective studies will be conducted that assess fewer variables based on the findings of this study.

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