Study Title: Handheld Infrared Thermometer to Evaluate Cellulitis (HI TEC) Cohort Study

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Introduction

Specific Objective(s) with hypotheses

The Handheld Infrared Thermometer to Evaluate Cellulitis (HI TEC) study is a pragmatic, prospective cohort study based at the McGill University Health Centre in Montreal, Canada. We hypothesize that skin surface temperature, as measured at the bedside with a handheld infrared thermometer, will have diagnostic utility in evaluating suspected cellulitis. We also hypothesize that a decrease in temperature differential between affected and non-affected skin will predict clinical response to treatment and could serve as a good surrogate marker for future clinical trials in cellulitis.

Primary Objective

1. To determine if the difference in skin surface temperature between a suspected area with cellulitis and non-affected areas is associated with an infectious disease physician's clinical diagnosis of cellulitis. An association would introduce a rapid, objective tool to help non-expert clinicians differentiate cellulitis from other non-infectious etiologies in the absence of subspecialty consultation. We hypothesize that the areas with cellulitis will have a higher surface temperature and be associated with a diagnosis of cellulitis as determined by the attending infectious diseases physician.

Secondary Objective

1. To determine if the change in surface temperature over the course of treatment for cellulitis is predictive of clinical response to therapy. A demonstrated association would allow clinicians to objectively assess treatment progress at the bedside as well as provide a good surrogate outcome in clinical trials. We hypothesize that the temperature

differential will decrease over the course of treatment and predict clinical improvement.

Background

Bacterial cellulitis is an infection of the skin and underlying soft tissue that is a leading cause of adult emergency room visits and an increasing cause of admission to hospital [1, 2]. As microbiological investigations are often uninformative [3], the diagnosis and management of cellulitis relies entirely on clinical judgment [4]. However, several non-infectious pathologies, including venous stasis, contact dermatitis, and lymphedema, can mimic the typical features of cellulitis [4, 5]. These mimics can lead to differences in diagnostic and therapeutic decisions among physicians [6]. Diagnostic uncertainty often results in antimicrobial use for non-infectious etiologies, which is estimated to cost up to $515 million annually in the United States and contributes to the burden of nosocomial infections, such as *C. difficile* [7].

An objective metric to differentiate cellulitis from its non-infectious mimics would be of significant clinical utility. Elevated skin surface temperature at the site of erythema, which is a hallmark feature of bacterial infection, is an intuitive potential metric. Recent trials of skin surface temperature have shown promise [8, 9], but no study has yet combined a pragmatic bedside measurement tool with an infectious diseases specialist's diagnosis and treatment plan. This is the basis of our proposal.

Innovation

If positive, our findings would have significant implications for both clinical practice and research. The practicality of the laser thermometer as a bedside diagnostic aid would reduce cellulitis misdiagnoses, improve patient outcomes, and optimize clinical resource use. Moreover, current Food and Drug Administration (FDA) guidelines specify that the primary efficacy endpoint of skin infection trials must be a precisely measured relative decrease in surface area of a lesion [10]. This is a cumbersome approach with minimal clinical utility and significant interobserver differences in measurement. If our results demonstrate that change in surface temperature predicts clinical response, this may become an alternative and more practical outcome measure for response to therapy which is robustly reproducible.

Methods

A prospective cohort study of patients seeking medical attention for suspected cellulitis

will be established. The Royal Victoria Hospital, the Montreal General Hospital and the Lachine Hospital (Montreal, Canada) will be the only participating sites.

Study Population

Inclusion Criteria:

- Age 18 years or older;
- English or French-speaking;
- Received an infectious diseases consultation to evaluate proven or suspected cellulitis of the upper or lower extremity, either unilaterally or bilaterally;
- Either no empiric antimicrobials received or, at most, antimicrobials begun within 24 hours of notification for enrolment.

Exclusion Criteria:

- Presumptive diagnosis of a soft tissue infection of the trunk, head or neck that does not also involve a limb;
- Patients with only one limb;
- Patients with significant neuropathies or autonomic syndromes that might affect thermoregulation, such as severe diabetic neuropathy or diabetic dysautonomia, neurologic neoplasms and known vitamin deficiencies;
- Soft tissue infections requiring definitive surgical source control, such as abscesses or necrotizing fasciitis.

Study Protocol

Our research team will be notified of eligible patients by direct page or e-mail from the infectious diseases service when a new consultation for cellulitis is requested. Within 6 hours of this notification (and ideally as soon as possible), we will obtain informed consent and enrol the patient. After obtaining informed consent, we will use a non-contact infrared thermometer to measure surface temperature at the site of suspected infection as well other locations on the ipsilateral and contralateral limb. Specifically, in the upper extremities, the surface temperature of the hand (mid point of dorsum) forearm (halfway point at the dorsal surface), and upper arm (approximately 10 cm below acromion process, middle of lateral portion or arm) will be measured in both limbs regardless of site of suspected infection. In the lower extremities, the surface temperature of the foot (mid point on dorsum of foot), shin (middle of leg, approximately 10 cm below tibial tuberosity), and distal thighs (approx. 10cm above superior edge of knee,

middle of thigh) will be consistently recorded. All measurements will be made in triplicate for the first ten patients and if there is very high reproducibility of the measurements in those ten single measurements from then on. If there is moderate to high reproducibility of the measurements we will reduce to duplicate.

Relevant laboratory and clinical information will also be extracted from the chart. Clinical information will include age, sex, medical co-morbidities, medications and clinical measurements (such as vital signs). Biochemical data will include white blood cell count and C-Reactive Protein levels (when available). Microbiological data, including cultures of blood and purulent exudate, will also be considered when available. Treatment data on which antibiotics and duration of therapy will be obtained but only after all initial measurements have been taken to avoid any potential bias in measurement. Treatment data will include the name of the ID physician (all ID physicians will agree via the Divisional Chair) so that appropriate statistical testing can be done to account for differences in the "gold standard" between doctors.

This data will be collected and managed using either the REDCap electronic data capture tools hosted at the McGill University Health Centre or another secure database system requiring password protected individually identified user accounts to access it [11]. Data will initially be stored by MRN (without name) but after all follow up visits are complete will be coded to ensure patient confidentiality (one-way hash of the MRN). The infectious diseases clinicians will be blinded to the result of the surface temperature measurement.

We will then compare the temperature difference between the affected and non-affected limbs with the current gold standard: the clinical diagnosis of the attending infectious diseases physician. This will yield estimates of sensitivity and specificity of the diagnostic test using expert clinical judgement as the gold standard.

In patients with cellulitis who are admitted for intravenous antibiotic therapy, we will perform daily measurements as described above throughout their admission. We will continue to record clinical data and laboratory data as above throughout admission for these patients. We will ultimately use statistical methods to characterize the relationship between skin surface temperature, expert clinical diagnosis of cellulitis and response to therapy (length of stay, duration of therapy, need for escalation in therapy, etc).

The study will be conducted until enrolment is completed. The anticipated study dates are September 1st 2018 to January 1st 2019.

Sample Size

In order to detect a 12% difference in skin surface temperature between limbs with a statistical power of 80%, assuming an alpha value of 5%, we anticipate that we will need to enrol 31 patients at a minimum. To be certain that we will establish reasonable sensitivity and specificity estimates and that our sample size will be sufficient, we will aim to enrol 50 patients with a diagnosis of cellulitis.

Statistical Analysis:

For our primary aim, classical 2 x 2 tables will be used to evaluate the sensitivity and specificity of skin surface temperature in predicting cellulitis, as diagnosed by the attending infectious diseases specialist. A temperature difference of 0.5°C between the area of suspected cellulitis and an average of non-affected areas will be considered significant in the first attempt.

With regards to our secondary aim, we will use multivariate analysis and logistic regression to determine relationships between change in temperature differential and clinical response. Response to therapy will be defined on the basis of clinical and laboratory data and will consider the following information:

- Days of fever (i.e the number of calendar days since enrolment in which a temperature of 38.0 or higher was recorded)
- Days of intravenous antimicrobial therapy for cellulitis
- Days of hospitalization for cellulitis (including days in the ER)
- Total number of days of antibiotics given for cellulitis
- Days to normalization of white blood cell count
- Days to normalization of C-Reactive Protein
- Patient reported outcomes:
    - Patient global impression of improvement scale
        - Select the option which best describes your cellulitis now, as compared to how it was when you arrived in the emergency department:
        - Very much better (1)
        - Much better (2)
        - A little better (3)
        - No change (4)
        - A little worse (5)
        - Much worse (6)
        - Very much worse (7)

Study Funding and Compensation

This study is not externally funded. The fees for purchasing the infrared thermometer will be borne by the investigators. Physicians and patients will not receive compensation for their participation in this pragmatic study.

References

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