Applying Systems Engineering to Improve Antibiotic Stewardship for Skin and Soft Tissues Infections in the Emergency Department

By

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Dedications

This dissertation is dedicated to all the teachers and mentors who supported my academic journey, my amazing wife (Dr. Nicole Rogus-Pulia) for always supporting and believing in me, my three sons (Michael, Luca, and Giovanni) for inspiring me, and my late grandmother (Dorothy Pulia, RN) for teaching me about the importance of hard work and following your dreams.

Prologue

Antimicrobial resistant (AMR) bacteria and associated infections represent one of the greatest known threats to global public health. These infections cause an estimated 1.27 deaths worldwide in 2019. Trend data indicate the prevalence of AMR is increasing at a time when the pipeline of new antimicrobial agents has been in precipitous decline. Given the direct link between consumption of antimicrobials and the development of AMR, extensive international efforts to reduce unnecessary and/or inappropriate antimicrobial utilization in healthcare and agricultural settings are ongoing.

Beyond public health considerations, the unnecessary and/or inappropriate antimicrobial utilization in healthcare settings represents a direct threat to individual patients. For instance, antimicrobials are among the most common causes of serious adverse drug events (ADE) and are the primary risk factor for the development of *Clostridioides difficile*, a life-threatening opportunistic infection of the digestive system that results in severe diarrhea and colitis. Vulnerable populations, including older adults and children, are particularly at-risk for harm related to these complications.

Initiatives aimed at improving antibiotic utilization in healthcare settings are termed Antimicrobial Stewardship Programs (ASP). The components of antimicrobial stewardship can be summarized by the '5 Ds': Diagnosis, Drug, Dose, Duration, and De-escalation. Diagnosis refers to making a correct assessment of whether or not the patient has an infection that requires antimicrobial therapy (necessary). Appropriateness refers to selecting the optimal drug, dose, and duration of therapy. Finally, de-escalation refers to tailoring of therapy in response to additional diagnostic information, typically in the form of organism culture data that is available hours to days after the initial patient encounter.

While ASPs traditionally have focused on hospitalized patients (inpatient settings), there is increasing recognition that ambulatory care settings, including the emergency department (ED), are also critical settings for these efforts. The majority of antimicrobials are prescribed in ambulatory settings and the ED is a frequent setting for unscheduled ambulatory care. The ED also serves as the entry point and setting of antimicrobial initiation for the majority of hospitalized patients. Diagnostic testing and treatment decisions made in the ED have significant implications for ASP efforts in downstream settings. For instance, misdiagnosis of infection in the ED can result in patients receiving days of unnecessary antimicrobial therapy and dosing errors in the ED are often perpetuated. De-escalation efforts depend on ED providers obtaining appropriate culture specimens, ideally prior to administration of any antimicrobials.

Skin and soft tissue infections (SSTIs), specifically cellulitis and abscesses, are among the most common bacterial infections encountered in the ED, comprising approximately 3% of all visits. The available literature indicates that these infections are frequently misdiagnosed in the ED and that guideline discordant antimicrobial prescribing is common among those with actual infections. Despite this, there is a paucity of literature exploring drivers of suboptimal antimicrobial prescribing for SSTIs and exploring potential solutions. Therefore, my dissertation work, summarized in this portfolio of three projects, utilized mixed-methods to address this critical knowledge gap. The foundation of this work is a systems engineering informed qualitative analysis of barriers to optimal antimicrobial use for SSTIs in the ED that yielded several target interventions. As diagnostic uncertainty was identified as the most influential barrier, the subsequent projects focus on identification of gaps in diagnostic assessment of cellulitis and examining the validity of thermal imaging as a novel tool to improve diagnostic accuracy in patients undergoing evaluation for cellulitis.

Chapter 1

Characterizing Barriers to Antibiotic Stewardship for Skin and Soft Tissue Infections in the Emergency Department Using a Systems Engineering Framework

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INTRODUCTION

Antibiotics are unique therapeutic agents often referred to as "societal" medications due to their ability to simultaneously impact the patient being treated and the community at-large.[1,2] Inappropriate use of antibiotics in healthcare settings is most often characterized as resulting from a failure to adhere to best practice guidelines and/or diagnostic error. This gap in care quality has been identified as a primary, modifiable contributor to the global increase in antibiotic-resistant bacterial infections.[3] Thus, there have been multiple "calls to action" related to antibiotic stewardship, including those targeting the emergency department (ED).[4]

Skin and soft tissue infections (SSTIs) account for approximately three percent of all ED encounters (>3 million annual visits) and available reports indicate frequent inappropriate antibiotic prescribing for this condition in this setting.[5–8] There is a clear need to identify interventions that can optimize antibiotic use in the management of SSTIs in the ED. In order to successfully improve prescribing, interventions must be informed by key drivers of behavior which can vary by provider type and setting.[9] While much is known about drivers of guideline discordant antibiotic use for other conditions (e.g. respiratory tract infections) and settings, the literature for SSTIs and the ED setting is comparatively limited.[10,11]

The International Federation for Emergency Medicine published a report characterizing the ED as a unique clinical environment in regard to quality and safety interventions.[12] The report emphasizes the need for human factors and systems engineering informed approaches to successfully overcome these barriers. Therefore, the purpose of this study was to characterize barriers and facilitators to optimal antibiotic use in the management of SSTIs in the ED using a systems engineering framework and map these to targeted stewardship interventions.

METHODS

Sampling

We conducted semi-structured interviews at a national emergency medicine (EM) conference. To achieve conceptual saturation, we conducted additional interviews with EM physicians working at university and community EDs in the Midwest.[13] To be eligible, physicians needed to be actively practicing clinical EM in the U.S. and have completed or be in the final year of an EM residency program. All participants received a financial incentive following the interview.

We recruited participants at the conference through conference emails and brochures included with conference materials. We also recruited participants from EDs near the study team by direct emails. We selected potential participants by purposeful criterion sampling to ensure we had representation of perspectives from a range of settings (urban, suburban, rural), geographic locations, years of experience, sex, and size of ED.[14] Interviews and analysis took place over a two-year period spanning from 2017-2019. Institutional review board approved all study activities.

Design and Procedure

We used semi-structured interviews to explore broad themes around the diagnostic and antibiotic decision-making process for SSTIs. Interview questions were primarily open ended so the participant could respond with what came to mind first. Follow up probing questions were based on elements of the SEIPS framework and utilized to identify themes within each element of the framework. (Supplement 1: Interview Guide). SEIPS was developed as a means to comprehensively assess elements of healthcare work systems that impact care processes and outcomes and has been successfully applied to characterize various quality of care and patient safety challenges (e.g. antibiotic stewardship and diagnostic errors).[15,16] The element at the

center of the model is the person (provider or patient) with surrounding elements being physical environment, tasks, organization, tools and technology, all of which operate within an external environment. The elements of the work system interact when preforming healthcare processes, which produce outcomes that feed back into the work system.

A non-clinical, female study team member with 5 years of experience in qualitative methods (RJS) conducted the interviews in a private room. The male principle investigator, a practicing EM physician with advanced training in systems engineering and qualitative methods (MSP), attended two of the initial interviews to observe, ask additional clarifying questions and facilitate minor modifications of the interview guide. We pilot tested the semi-structured interview guide with two EM physicians at our institution. As interviews progressed we refined questions and incorporated more pointed follow up questions to encourage physicians to elaborate on the emerging themes.

We audio recorded all interviews, which lasted an average of 48 minutes. Prior to starting the interview, we asked physicians demographic (sex and years of experience) and practice setting questions (type of ED, teaching versus non-teaching, the annual ED volume per year and the geographic region of the country where they worked). We proceeded with sampling, data collection and data analysis concurrently and stopped data collection when sufficient heterogeneity in participant answers was achieved as determined by the responses becoming redundant and targeted probes failing to uncover new themes (i.e. conceptual saturation).[13] A private company professionally transcribed audio files verbatim and the study team reviewed them for accuracy.

Analysis

We used deductive directed content analysis guided by the SEIPS model.[17] RJS wrote an initial memo after each interview to capture emerging concepts and general observations that was utilized as we generated the codebook.[18] The study team developed a preliminary codebook based on the domains of the interview questions and the elements in the SEIPS model.[19] Two study team members (MSP and RJS) used the preliminary codebook and coded six interviews independently. Next, the coders met to review codes, add new codes and refine code definitions. The study team continued to use memos during the coding process as a way to track how code definitions evolved and divergent cases. We conducted this process for six interviews. For the remaining interviews, RJS completed primary coding with MSP conducting a secondary review and adding additional codes as needed. Any discrepancies in coding were resolved by discussion and consensus.[20] Finalized codebook is included as Supplement 2. We used Dedoose, qualitative data software, to facilitate the coding process.[21]

Once coding was complete, we generated a list of codes representing modifiable barriers and facilitators. This list was mapped to a series of targeted interventions that were presented to a diverse group of twelve stakeholders in small groups and individual meetings to elicit feedback. Stakeholders included emergency clinicians (physicians, residents, and mid-level providers), ED nurses, leaders of the ED clinical operations team, and antibiotic stewardship leaders from infectious diseases and pharmacy. The meetings ranged from 20-40 minutes in length and suggestions on the proposed interventions were captured by detailed notetaking. Revisions of the interventions and associated descriptions continued until there was group consensus that no further edits were necessary.

RESULTS

In total, we had 39 physicians express interest in participating and we conducted 20 interviews. No one refused to participate. The demographic and practice setting characteristics are summarized in Table 1. The results that follow are organized according to the primary work system code of the SEIPS model with the last section of the results describing cross-cutting themes and mapped interventions.

Barriers

We identified barriers to optimal antibiotic prescribing within the person (provider and patient), task, organization, tool and technology and external-environment work-system elements of the SEIPS framework (Table 2).

Person-level Barriers

Physicians described how patient expectation of treatment for both cellulitis and abscess was a barrier to optimal antibiotic prescribing because it led physicians to give patients antibiotics even if they did not always think they were necessary (Q1, Q2). Physicians described an increased willingness to prescribe antibiotics and to prescribe multiple antibiotics for SSTI for patients who have an increased risk profile (e.g. diabetes, recurrent infections), even if there was considerable diagnostic uncertainty (Q3, Q4). Providers also described how provider fear of treatment failure, including the development of a more serious infection with delayed treatment (e.g. sepsis) and bounce backs were barriers to optimal antibiotic prescribing (Q5, Q6). Concerns over the chance of treatment failure were prioritized over the potential harms related to unnecessary antibiotics. (Q7, Q8).

Task-level Barriers

Diagnostic uncertainty was one of the primary barriers to optimally utilizing antibiotics for cellulitis. Physicians described utilizing antibiotics for a suspected cellulitis even if they had low

levels of diagnostic certainty (Q9-Q11). Physicians described how optimal antibiotic usage for cellulitis was challenging because there is no objective diagnostic test (Q12). For abscess, diagnostic certainty was not a barrier except as it related to not knowing if the causative organism was methicillin-resistant *Staphylococcus aureus* (MRSA). This uncertainty often led to the prescription of multiple antibiotics to achieve expanded spectrum of coverage (Q13, Q14).

Organization-level Barriers

Physicians described an organizational culture where it is unacceptable to miss a bacterial infection (Q15). This culture encouraged physicians to 'err on the side of caution' and prescribe in cases of diagnostic uncertainty. Specifically, physicians cited pressure from hospital or department administration to do something for patients which was a barrier to optimal antibiotic utilization (Q16). This pressure was particularly apparent when providers' institutions emphasized patient satisfaction scores and if the provider believed the patient expected antibiotics (Q17). Physicians described poor access to ED follow up care as a barrier to optimal antibiotic utilization because in many cases they could not count on a patient being seen for reevaluation in a day or two and were thus more likely to treat these patients with antibiotics in the ED (Q18). Finally, physicians described how time pressures in a busy ED was a barrier to optimal antibiotic prescribing because they simply did not have time to talk with patients about appropriate antibiotic use, including risks and benefits. Often it was perceived as easier to give a patient the antibiotic versus engaging in a lengthy conversation about the decision-making process. (Q19).

Tool and Technology-level Barriers

Physicians also described the need for diagnostic tools and how the absence of these tools made it hard to optimally diagnose SSTIs. For abscess, physicians were interested in having a rapid

diagnostic test that could detect the presence of MRSA (Q20). Likewise, for cellulitis, physicians described the need for new tools to help them accurately diagnose cellulitis (Q21).

Environment-level Barriers

There were several external environment barriers to optimal antibiotic prescribing. There was a sense by many physicians that the current standard of practice in EM is to utilize antibiotics to treat cellulitis if there is any degree of clinical suspicion, and that it is challenging to go against historical standard of practice (Q22). Likewise, with abscess, many physicians described equipoise in the literature regarding the optimal utilization of antibiotics, which can make it hard for physicians to know how to optimally utilize antibiotics (Q23).

Facilitators

The physicians also described person and task-level facilitators (Table 3).

Person-level Facilitators

Many physicians described having a shared decision-making conversation with patients. They felt that if they had enough time, they could often get buy-in to plans that did not involve prescribing an antibiotic (Q24). This contrasts with the patient expectation barrier described previously where many physicians felt like patients always expected antibiotics no matter how much they discussed the idea of not prescribing with patients. A second person-level facilitator was physicians who self-identified as 'antibiotic stewards'. These physicians expressed the importance of antibiotic stewardship and in cases of uncertainty were more likely to consider the risk to benefit ratio related to antibiotics. This resulted in being more selective with prescribing out of concern for potential harm related to antibiotics and contributing to bacterial resistance in their hospital and community (Q25, Q26).

Task-level Facilitators

Physicians described many task-level facilitators that helped them optimally prescribe antibiotics for skin infections. For abscess, physicians described how they could routinely convince patients that they did not need an antibiotic after completing an incision and drainage because they had done an intervention, drained the infection (Q27). For cellulitis, ruling out mimics was a facilitator that physicians used to help them optimally use antibiotics. Physicians said that they would utilize patient history, physical exam, lab values and imaging results to work through a process of elimination where they ruled out common mimics before settling on a cellulitis diagnosis and antibiotics (Q28). Additionally, physicians described using the facilitator, watchful waiting, where they would not give a patient an antibiotic but instead put in place a plan for a recheck if the infection worsened (Q29). Finally, some physicians described providing a wait and fill prescription where they would prescribe an antibiotic so the patient did not have to come back to the ED, but would instruct the patient only to take it under certain circumstances such as they spiked a fever or the symptoms continued to progress (e.g. expanding erythema) (Q30).

Intervention Mapping

We selected potentially modifiable barriers and operationalizable facilitators identified by the physicians and mapped them to interventions that could mitigate the barrier or enhance the facilitator (Table 4). These barriers cut across many of the identified SEIPS work system elements and included lack of access to ED follow-up care; patient expectations; diagnostic uncertainty (MRSA and pseudocellulitis); fear of adverse outcomes, perceived clinical equipoise, and provider knowledge gaps. The interventions mapped to these ranged from systems level programs (e.g. community paramedicine follow-up programs) to novel diagnostics and clinical decision support tools. Each intervention has a detailed description which was designed for use in a follow-up clinical vignette based discrete choice experiment.

DISCUSSION

In this analysis, we present the first qualitative assessment of perceived barriers and facilitators to optimal antibiotic prescribing for SSTIs from the perspective of emergency physicians. Utilizing a systems engineering framework (SEIPS) enabled us to identify barriers beyond the patient and provider themselves. This directly addresses calls to develop quality improvement interventions (e.g. antibiotic stewardship) that are grounded in systems engineering and behavior change theory and informed by data collected from frontline providers.[9,22–24] Key identified barriers to optimal antibiotic prescribing for SSTIs included poor access to follow up care (organization), need for more definitive diagnostic tools (tools & technology) and fear over adverse outcomes related to missed infections (person).

One unexpected finding for our analysis was the identification of knowledge gaps and skepticism of the literature involving optimal antibiotic stewardship for SSTIs. For instance, many providers held the view that antibiotics should now be given to all patients based on more recent trial data. There was a lack of awareness about the high number needed to treat in these trials and recent calls for a more nuanced approach to antibiotic prescribing for uncomplicated abscesses.[25,26] Additionally, most providers doubted the validity of literature citing a 30% misdiagnosis rate of cellulitis in the ED.[7] One potential technological solution to these knowledge gaps would be clinical decision support embedded in the electronic health record as best practice alerts. These would in effect raise awareness of findings from recent studies and opportunities to optimize antibiotic stewardship in the management of SSTIs.

SSTIs pose a particular diagnostic challenge given the absence of a gold standard test. Providers expressed that the treatment decision must be made despite significant diagnostic uncertainty. Most providers opted to ‘err on the side of caution’ which involved prescribing an antibiotic(s)

even if the perceived likelihood of bacterial infection and/or their diagnostic certainty was low. This was especially true when other barriers were present such as poor access to follow up care or a high-risk patient profile, which essentially lowered the bar to prescribe an antibiotic. The perceived patient and professional risk related to failing to provide antibiotics for an actual SSTI typically outweighed the acknowledged risk of adverse drug reactions and detrimental impact on public health related to unnecessary antibiotic use. Providers felt that evidence based diagnostic tools that would make the SSTI evaluation process more objective would be enable them to avoid prescribing in cases of low clinical suspicion.

Interestingly there are evidence-based interventions that would fit this need that have not been extensively studied or adopted. For instance, rapid MRSA assays for purulent infections that strongly correlate with traditional cultures and improve tailored prescribing have been available for years.[27] Although not as well established, risk stratification scores (ALT-70) and surface thermal imaging have demonstrated potential to accurately differentiate cellulitis from pseudocellulitis.[28,29]

The perception among providers that patients often expect antibiotics has been documented across a variety of healthcare settings, including the ED.[11,30] However, research examining actual patient expectations in the ED did not find that patients routinely expect antibiotics.[11,31] In addition to encouraging providers not to assume all patients expect an antibiotic, a potential intervention would be for healthcare organizations to exclude encounters involving demands for non-indicated antibiotics from patient satisfaction metrics. Alternatively, a more patient centered approach towards education and shared decision making could potentially avoid this issue altogether. The development of a shared decision making tool to facilitate patient-provider communication, such as has been demonstrated effective in reducing low value workups for low

risk chest pain in the ED, could enable clarification of the patient's actual expectations (if any) while educating them about their individual risk and the providers level of diagnostic certainty (or lack thereof).[32,33]

External environment related barriers need to be addressed at a healthcare system level. For instance, providers often 'lower the bar' to treat patients who have known difficulties with access to follow up care. Ensure that the patient could have a repeat assessment in a timely fashion to ensure any progression of the condition is identified as soon as possible could increase provider comfort in withholding antibiotics. With the rapid expansion of telehealth services due to the COVID-19 pandemic, it is more feasible than ever to incorporate either synchronous or asynchronous follow-up visits into ED SSTI care protocols.

This study had several limitations. Our recruitment strategy was an opt-in system, and it is possible that physicians who were already informed and interested in managing infections in the ED were the participants in the study. The proposed interventions were based on a mapping process to the identified qualitative themes, and we were not able to ascertain the magnitude of their potential impact.

Conclusion

Using a systems engineering informed qualitative approach, we were able to characterize a number of barriers and facilitators to optimal antibiotic use for SSTIs specific to the ED work system. The developed mapped interventions span multiple components of the ED work system and should inform future efforts to improve antibiotic stewardship for SSTIs in this setting.

Table 1. Description of Physician and Practice Setting Characteristics (n=20)	
	n (%)
Female	9 (45%)
# Years Post Residency	
0 (Still in Residency)	2 (10%)
1-3	3 (15%)
4-9	9 (45%)
10-14	0 (0%)
15 or more	6 (30%)
Setting	
Urban	9 (45%)
Suburban	7 (35%)
Rural	4 (20%)
Type of ED	
Community	13 (65%)
University	4 (20%)
Government System	3 (15%)
Teaching vs. Non-Teaching ED	
Teaching	11 (55%)
Non-Teaching	9 (45%)
Average Annual ED Volume	
20,000-39,999	4 (20%)
40,000-59,999	3 (15%)

	60,000-79,999	6 (30%)
	80,000-99,999	5 (25%)
	≥ 100,000	2 (10%)
Geographic Location in the US		
	Midwest	4 (20%)
	Northeast	3 (15%)
	South	8 (40%)
	West	5 (25%)

Table 2. Barriers to Optimal Antibiotic Prescribing, Corresponding Work System Element, Infection Type and Representative Quote				
Barriers	Primary Work System Element	Secondary Work System Element	Infection Type	Representative Quote
Patient Expectations	Person	Task	Both*	Q1. Everybody's expectation are that they are treated with some type of antibiotic. So as far as cellulitis goes, I do give them antibiotics. Sometimes I will give them a short course, you know, not a prolonged amount of time. But that's their expectations, unfortunately. I don't agree with it, and I try to educate them, I try to do that. But, unfortunately, you can spend 20 minutes educating someone and they'll still say well, where's my prescription? (EP017)
				Q2. There is some component of feeling pressured by the patients to do something about it and not just say, put a warm compress, or take Tylenol or Motrin. So I think that plays a factor as well (EP001)

High-risk patient profile	Person	Task	Both	Q3. If it's recurrent, if it looks bad, and you're going to send them out, then we'll put them on a [dual therapy]. (EP008)
				Q4. Usually, I will err on the side of caution to treat if they have other risk factors, especially for a diabetic. (EP006)
Provider Fear of Adverse Outcomes	Person	External Environment	Both	Q5. I would say that there are patients that I don't think the antibiotics are really going to help, but I'll still put them on because of risk of bounce-back or risk of it getting worse. (EP008)
				Q6. I think probably the biggest one is the fear of progression to sepsis, you know, sepsis has significant morbidity and mortality, so the bounce back of a patient who you discharged with a significant cellulitis and came back septic, and, you know, diabetic and dies from septic shock. (EP014)
Prioritization of Proximal Complaint	Person	External Environment	Both	Q7. So the general public theoretical concern is of no interest to me… Because I'm only concerned about, I

over Potential Consequences of Antibiotics				only have one responsibility when I'm taking care of a patient, and that's the patient. That's it. (EP013)
				Q8. How do you weigh your decision on an individual patient versus ten years from now? So the answer is, sure, it does bother me at times, absolutely but my immediate concern is the patient. I mean we don't always do the right thing for the patient and we overprescribe, absolutely. (EP012)
Diagnostic Uncertainty	Task	Person	Cellulitis	Q9. I think, the two big questions are, am I going to treat this, and then what coverage am I going to select? Physicians aren't great at telling if it's cellulitis or not and often we end up 60% or 70% sure something is cellulitis or maybe even less so. Venous stasis can look a lot like cellulitis. But if somebody comes in, and they're saying they have new pain, and they have some other infectious symptoms, often we will treat it as cellulitis even if we're not particularly convinced this is 100% cellulitis. So I

				think the treatment threshold is relatively low for providing antibiotics. (EP018)
		Organization		Q10. If I've ruled out every other alternate diagnosis, and cellulitis is what's left, I would put them on antibiotics and have them follow up with their primary doctor in a few days to see if it's improved. If it's not improved, then perhaps there's more clinical signs that have shown in that mean time, and then their primary doctor could decide to take them off antibiotics or continue. (EP019)
		Person		Q11. Those cases where it looks like it, and I'm worried about it, and I'll treat it, but and because we don't have any definitive tests, and you have to use your clinical judgment. But that's always in the back of my mind. Does this patient really need this? (EP005)
No Clear Diagnostic Test	Task	Tools & Technology	Cellulitis	Q12. Just keep in mind, it's very subjective….There's no good lab study out there to tell us one way or the other. (EP014)

Concern for MRSA	Task	External Environment	Abscess	Q13. But unfortunately, the communities that I've always worked at, the MRSA is pretty high, so unfortunately, I usually go beyond just giving Keflex (EP001)
		Person	Abscess	Q14. You have to take into account the risk of the patient. If they're immunosuppressed diabetic, on and on and on, then and the other factor is whether you suspect it to be a MRSA. If it's a recurrent abscess, cutaneous abscess more suspicious of MRSA, then I might treat it. (EP013)
Unacceptable to be Wrong	Organization	Task	Both	Q15. The concern that, you know, the patient may get worse. It's all a guess. I mean, the, like most of cellulitis management is just intuition guessing and educated guessing. And so, you know, we're not allowed to be wrong ever. It's not acceptable ever to be wrong. (EP013)
Emphasis on Patient Satisfaction Scores	Organization	Person	Both	Q16. I feel sometimes like I am overprescribing. And as I mentioned before, I feel sometimes a lot of pressure from the patients and

				administration to prescribe when in fact the patient doesn't really need it. (EP001)
				Q17. If it looks like a little small nothing that you're opening it up, I may not give them or you may give them Keflex because they're not satisfied, you know. It's like I don't know if they use Pres Ganey where you are, but then they give you a bad Pres Ganey because you didn't give them an antibiotic (EP004)
Access to Care	Organization	External Environment	Both	Q18. …But with primary care the way it is and with patients without insurance, yeah, it's concerning. So I'm going to err on the side of treatment. (EP012)
Time Pressures/ ED Crowding	Organization	Person	Both	Q19. If you don't have time, because you're in a very busy ER with, you know, hall beds and people in the waiting room. I feel like it becomes a secondary thing, and people have an expectation and taking the time to convince them that they don't need it becomes challenging. (EP015)

Rapid Diagnostics	Tool & Technology	Internal Environment	Abscess	Q20. If I had like a rapid PCR for MRSA, I'd use that, or if we, even a nasal swab, you know, that came back. The problem is, in an emergency setting, it would have to come back in a rapid fashion. I wouldn't use it on every patient, but on my patients where I had clinical uncertainty, I would definitely rely on that. (EP020)
More Definitive Diagnostic Tests	Tool & Technology	Task	Cellulitis	Q21. I think we would probably love if there was some sort of, as close to definitive as you can get way of figuring out whether it truly, you know, whether it's scoring systems or pathways, of determining whether it is a cellulitis or whether this is not a cellulitis. (EP014)
Standard of Practice	External Environment	Task	Both	Q22. I would say there are clear barriers. I think there is the barrier of almost expectation, not only from the patient but from like a historical standpoint. I mean, you know, you have what appears to be or is concerning for cellulitis, that is something that people treat with

				antibiotics, and I think that's just the known historical thought. I think there's almost a point of like a standard of care. (EP015)
Equipoise in the Literature	External Environment	Task	Abscess	Q23. I think if someone requested or demands it, I'll have a talk with them about the risks and benefits. You know, again because it's such an area of equipoise with the abscesses, it's hard for me to say like, if I've explained risks and benefits and somebody is like, I don't care about diarrhea, I want to make 100% sure this doesn't come back, I'm willing to take the risk and take antibiotics. (EP018)
*Both includes cellulitis and abscess				

Table 3. Facilitators to Optimal Antibiotic Prescribing, Corresponding Work System Element, Infection Type and Representative Quote

Facilitators	Primary Work System Element	Secondary Work System Element	Infection Type	Representative Quote

Shared Decision Making Conversation	Person	Organization	Both	Q24. So I would say that most of the time in my primary job, I can get buy-in for the mimic and I can also get buy-in for we're going to give this a trial if I actually have time to talk to patients. So I try to talk about diarrhea, C. Diff and yeast infections and that's why we try to hold off. Plus if you get this again and it is a cellulitis, then we really want to be able to have the antibiotic for you at that point in time. (EP015)
Identifying as a Steward of Antibiotics	Person	Task	Both	Q25. I think I'm a pretty good steward of antibiotics… giving the right antibiotic for the right thing and not giving antibiotics when they're not indicated (EP002)
				Q26. People get recurrent MRSA abscesses, and they get an antibiotic every time. But I'm actually more concerned about that patient, because they're at risk for developing resistant organisms to the very drugs that they may need in the future, you know, when they become elderly and immunosuppressed and diabetic and things. So I will actually be closer stewards of antibiotics in their case,

				and if it's a discrete abscess, be like I really don't want to put you at risk for drug resistant organisms. (EP020)
Explaining the Potential for I+D Alone to Cure	Task	Internal Environment	Abscess	Q27. For this situation, they tend to respond pretty well because the difference that I would explain to them between me and their primary doctor is I have the time to do the I+D, which is going to fix them. So most of the time, you explain it to them. They're just happy that the thing is gone. That's their ultimate goal. (EP002)
Considering Cellulitis Mimics	Task	Person	Cellulitis	Q28. So you've got the textbook, right, redness, warmth, venous tracking, fluctuance or signs of abscess, fever, systemic illness. So that's kind of the basis, the basic level. And then you've got the patient in front of you, who didn't read the textbook and could have any mixture of those symptoms or partial symptoms. And my initial approach is to really make a commitment to whether I think this is cellulitis or not, and that's based on ruling out mimics. So I want to make sure it's not peripheral arterial disease where it's

				bilateral, shiny skin, not really feeling warm, something like that, or chronic venous insufficiency and lymphedema leading to some skin changes. So there are definitely cellulitis mimics out there. And I just want to, I guess it's a process of elimination saying, okay, I don't think this is a mimic. I think it's a cellulitis. (EP020)
Watchful Waiting	Task	Organization	Both	Q29. Yeah sometimes, I think it is not as likely a cellulitis…if we're doing kind of like a watchful waiting with someone that has a very early case of skin irritation, then if I know they have a primary care doctor, they can go there. If they don't, I just have them come back to the ER. (EP007)
Wait and Fill Prescription	Task	Person	Both	Q30. If someone comes in and feels very, very strongly that they need antibiotics and I don't feel like they do, I'd probably use the strategy of here's a prescription. Please wait a day, see if it progresses, and then you can use it. (EP019)

Table 4: Mapped Skin and Soft Tissue Infection Stewardship Interventions for the Emergency Department				
Barrier	Infection Type	SEIPS Work System Element(s)	Mapped Intervention	Intervention Description
Lack of Access to ED Follow-up Care	Both	Organization and External Environment	Telehealth or community paramedicine program for reliable outpatient follow up	The emergency department can arrange 24-hour follow-up for discharged patients by either an in-home visit by a community paramedic or a virtual appointment using an online, video enabled telehealth system.
Patient Expectations	Both	Person	Exclude encounters involving inappropriate	Your hospital quality department allows you to flag cases involving

			antibiotic requests from satisfaction metrics	inappropriate requests for antibiotics and these are excluded from your patient satisfaction metrics.
Diagnostic Uncertainty (MRSA)	Abscess	Tools and Technology, Tasks	MRSA PCR of purulent infections	Your laboratory offers rapid (~90 minute) turnaround time for assay capable of detecting MRSA in purulent material from the I+D procedure (negative predictive value = 95%).[27]
Diagnostic Uncertainty (Pseudocellulitis)	Cellulitis	Tools and Technology, Tasks	Clinical decision score (ALT-70) and/or thermal imaging camera	A thermal imaging camera indicates the maximum skin surface temperature of the affected leg is identical to the

				unaffected leg. The average reported skin temperature difference for cellulitis is 3.7ºC greater in the affected limb.[28]
Fear of Adverse Outcomes	Both	Person, External Environment, Organization, Internal Environment	Shared decision making tool	The tool will facilitate a more efficient, less time-consuming conversation about risks and benefits of antibiotics for the particular clinical scenario.
Perceived Clinical Equipoise	Abscess	Person, Tools and Technology, Tasks, Organization	Clinical decision support/Best Practice Alert	Your electronic health record has alerted you that this condition can potentially be managed without

				antibiotics in the majority of cases (Number needed to treat (NNT) with antibiotics to prevent 1 treatment failure = 14-26). No serious complications observed in placebo group of uncomplicated abscess trials. [25,36,37]
Provider Knowledge Gaps	Cellulitis	Person, Tools and Technology, Tasks, Organization	Clinical decision support/Best Practice Alert	A best practice alert in the electronic health record has triggered the following message, "Studies indicate up to 30% of cellulitis cases diagnosed in the emergency department are

				actually misdiagnosed mimics which do not require antibiotics.”

Chapter 2

Comparing Skin Surface Temperature to Clinical Documentation of Skin Warmth in Emergency Department Patients Diagnosed with Cellulitis

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BACKGROUND

Cellulitis, a common bacterial skin infection is overdiagnosed in up to 30% of cases due to the presence of mimicking, non-infectious pathologies termed pseudocellulitis.[7,36] Associated diagnostic errors result in antibiotic overuse which poses a threat to patient safety and public health.[7,37] As cellulitis is primarily a clinical diagnosis, physicians must heavily rely on the reported history and subjective physical exam findings.[38] One such finding is whether or not a patient exhibits excess skin surface warmth in the area of concern.

Skin surface warmth is a commonly reported feature of cellulitis, resulting from the body's innate immune response following infection, often caused by *Streptococcus pyogenes* or *Staphylococcus aureus.*[38] In response to bacterial invasion, cytokines and granulocytes are recruited which triggers an epidermal response. Increased vascular permeability and blood flow within the skin combined with heightened metabolic activity raises the temperature of the affected skin and increases the rate at which thermal energy transfers to the surrounding air.[39]

With this in consideration, thermal imaging has been explored as a means to objectively characterize skin surface temperatures of patients presenting with potential cellulitis. Ko et al. found that cellulitis and pseudocellulitis patients had average maximum affected skin temperatures of 34.1°C and 31.5°C ($p = 0.008$), respectively.[28] They concluded that the observed temperature differences could improve differentiation of cellulitis and pseudocellulitis and reduce diagnostic errors.

Although the assessment of skin surface warmth is considered a key component of the clinical evaluation for potential cases of cellulitis, the extent to which warmth is currently reported by patients and documented by emergency providers is unknown. Therefore, the objective of this study was to compare clinically-documented [history of present illness (HPI)

and physical exam] and patient-reported skin warmth to surface thermal imaging obtained quantitative skin surface temperatures in patients diagnosed with cellulitis in the emergency department (ED). We hypothesized that the frequency of skin temperature clinical documentation would increase as measured skin surface temperatures increased due to increased detection.

METHODS

Patient Selection

This study was reviewed and approved by the local Institutional Review Board and was part of a larger validation study that aimed to compare skin surface temperatures of cellulitis and pseudocellulitis patients. Patients 18 years and older presenting to the ED with a chief complaint related to a visibly erythematous lower extremity were prospectively enrolled upon written consent from October 2018 to March 2020 at a quaternary care center in the Midwest. Of these patients, only those who had a final diagnostic impression of cellulitis or assigned ICD code for cellulitis plus received antibiotic therapy for cellulitis, as indicated on the order, were included in this analysis. Patients were excluded if their chief complaint resulted from acute traumatic injury within the past 5 days, if the skin changes were present on both legs (bilateral) or exclusive to the toes, if the affected area included a confirmed fracture or an implant/hardware, they applied ice or heat within the past hour, or if the area included a recent surgical site (past 4 weeks). Additionally, patients were excluded if they were non-English speaking, pregnant, a prisoner, or had impaired decision-making.

Baseline Data Collection

During the ED encounter, trained research coordinators collected baseline patient demographics such as age, race, biological sex, and ethnicity. Additionally, patients were asked

detailed symptom inventories, including if they had been experiencing excess warmth in their affected area of skin related to their acute complaint. All these questions were asked prior to obtaining the thermal images.

Thermal Imaging Data Collection

Surface temperature images were taken of the patient's affected area of skin and the exact corresponding area on the contralateral extremity (unaffected control limb) with a FLIR One thermal camera (Generation One, FLIR Systems) attached to an iPad from a distance of ~30 cm). This camera measures surface temperatures ranging from -20°C to 120°C without direct contact and detects temperature differences as small as 0.1°C.[28]

All thermal images were stored on a secure computer and FLIR Tools (Tools+ 5.13) was used to manually select areas of interest within the thermal images to derive the average temperature (Tavg) of each patient's affected and corresponding unaffected area of skin. The temperature difference between these two areas [Tavg affected (°C) – Tavg unaffected (°C)] was defined as the patient's temperature gradient (Tgradient). Patients with a Tgradient > 0°C were considered to have objective warmth in their affected area. All data were collected and stored in REDCap.

Data Extraction from Electronic Health Record

Structured chart review was done to manually abstract the documentation of skin temperature in the history of present illness (HPI) and physical exam. Prior to beginning chart review, all abstracted variables were clearly defined and their definitions were documented in a study codebook. Data abstraction forms were setup using REDCap software, and research coordinators, who were blinded to the study's hypothesis, were trained on the first 20 charts to ensure consistent data abstraction. Abstraction performance was monitored by double-abstracting

15% of charts (randomly selected) and checking for consistency in responses. Routine check-in meetings and frequent email communication were utilized to clarify questions about specific patients.

For abstracting clinically-documented warmth, keywords or phrases suggestive of increased warmth (e.g. “warmth noted”, “right leg warmer than left”, “warm to the touch”, and “hot”) were considered documentation of an elevated skin surface temperature. The skin exam macro templates used by the group, “warm and dry” and “warm and well perfused”, were not considered specific documentation of an elevated skin surface temperature.

Data Analysis

McNemar’s test was used to compare patient report with clinical documentation (HPI and physical exam) for patients with objective skin surface warmth. Chi-square was used to compare patient report and clinical documentation of warmth across increasing Tgradient by sorting cases as follows: >0 to 1°C, >1 to 2°C, >2 to 3°C, >3 to 4°C, >4 to 5°C, and >5°C. Two-sided t-tests were used to compare differences in average affected Tavg and Tgradient when warmth was both present and absent in the patient report, HPI, and physical exam. All data were analyzed in STATA (Stata/SE 16.1).

RESULTS

From October 2018 to March 2020, 126 patients diagnosed with lower extremity cellulitis met inclusion criteria. This final cohort was 37% female, 87% White, had an average age of 55.4 years, and 56% were discharged from the ED (Table 1). A total of 110 (87%) cases exhibited objective skin surface warmth (Tgradient > 0°C). In cases where objective skin warmth was present median Tgradient was 2.6°C and the interquartile range was 1.6°C to 4.5°C. Of these cases, 58 (53%) had warmth documented in their physical exam. Additionally, 86 (78%) of

patients reported warmth when asked by the study team while only 7 (6%) had warmth documented in their HPI (difference 72%, 95% CI: 62% to 82%; $p < 0.001$). A total of 16 (13%) of cases had no objective skin warmth. In these cases, median Tgradient was -1.0°C and the interquartile range was -1.6°C to 0.65°C. Of these cases, 7 (44%) had warmth documented in the physical exam, 12 (75%) reported warmth to the study team and 0 (0%) had warmth documented in their HPI.

No association was found between increasing Tgradient and patient report ($p = 0.893$) or clinical documentation ($p = 0.483$) (Figure 1). No significant differences were found between average Tgradient when warmth was documented versus not documented in the patient report, physical exam, or HPI. Additionally, no significant differences were found between Tavg when warmth was documented versus not documented by patient report or in the HPI. However, a significant difference was found between Tavg affected when warmth was documented (32.1°C) versus not documented (31.0°C) in the physical exam (difference = 1.1°C, 95% CI: 0.29 to 1.94; $p = 0.0083$) (Table 2)

Limitations

This was a single center study and documentation practices for cellulitis may vary significantly based on local practice patterns. As the clinicians were not asked if they assessed for or perceived skin surface temperature elevation, we can only comment on what was documented and not what actually may have occurred during the encounter. In light of the aforementioned limitation, we are unable to exactly determine the factor(s) driving the observed discrepancies. Finally, as ED overdiagnosis of cellulitis is reported in the literature, it is possible that some cases in the analysis would not be deemed cellulitis upon secondary review.

DISCUSSION

Elevated skin temperature is considered a key feature of cellulitis diagnosis, yet the extent to which this is captured as part of the HPI, detected on physical exam, and documented by providers is unknown. To our knowledge, this is the first study to examine skin temperature documentation practices in the ED and compare them to both patient-reported warmth and quantitative skin surface temperatures measured by surface thermal imaging.

Results indicate the vast majority (87%) of ED-diagnosed cellulitis cases exhibit objective warmth (Tgradient > 0°C). Based on the previously-established ED cellulitis misdiagnosis rate of 30%, the percentage of true cellulitis cases that exhibit objective warmth is likely higher. This notion is supported by the findings of Ko et al. that objective warmth was present in 96.6% of dermatology-diagnosed cellulitis.[28] This reaffirms the traditional clinical teaching that increased skin warmth is a reliable diagnostic feature of cellulitis.

Although surface thermal imaging demonstrated objectively-elevated skin temperature in the majority of cases, clinical documentation was inconsistent. Most notable was that while 78% of patients with measured skin warmth reported experiencing warmth in the affected area of skin, only 6% had this documented in their HPI. As the clinical history is a key component of the diagnostic process, this finding may partially explain the reported diagnostic errors rates for cellulitis. [7,36,38,40] This finding reflects observations by Caterino et al. that ED patient self-reported infection related symptoms are often missing from the clinical documentation.[41,42] While we recommend improved questioning through direct inquiry and documentation of patient-reported skin warmth in all cases of suspected cellulitis, it is interesting that patient report was not associated with objective temperature measures.

Regarding the physical exam, a significant difference was found in the Tavg of affected skin when warmth was documented. This finding suggest that when ED providers detect and

document warmth, patients' affected skin surface temperature is higher on average. Unsurprisingly, the physical exam appears to be a more reliable means of assessing skin warmth than patient report. However, only 53% of patients with objectively measured increased skin temperature had warmth documented in their physical exam. While this number is better than patient-reported warmth or documentation of warmth in the HPI, it still raises concern over either inconsistent assessment, inability to detect warmth, or inadequate physical exam documentation of skin temperature in cases of suspected lower extremity cellulitis. A study by Tse et al. found that physicians detected a > 3.0°C difference in extremities only 75% of the time.[43] This failure to detect a significant number of cases despite a high temperature gradient raises concerns about the reliability of warmth detection during the physical exam, particularly when lower temperature gradients are involved. Our findings suggest that this is not solely a detection issue since clinical documentation did not increase as skin surface temperature gradients increased. One would assume the ability to sense elevated skin temperature by touch would increase along with the actual temperature, however, this was not our observation. Further study of temperature detection limits by touch are needed to clarify the optimal clinical scenario for use of objective skin surface temperature measurement.

In conclusion, the observed inconsistencies between patient report, clinician documentation, and objective skin surface temperature measurements indicate the need for improved documentation and tools to objectively quantify skin warmth in patients with potential cellulitis. Cellulitis is commonly misdiagnosed in the ED which leads to unnecessary use of antibiotics.[7,36] Increased tissue warmth is a classic feature of cellulitis that can be used to differentiate it from mimics. However, our results suggest there are significant challenges to the assessment of warmth in this population. While available data suggest objective temperature data

obtained from surface thermal imaging cameras can differentiate cellulitis from pseudocellulitis, there needs to be further validation of this technology and evaluation of its impact on diagnostic accuracy.[43,44] Developing interventions that can reduce diagnostic error in the evaluation of cellulitis is an important patient safety and public health objective.[37]

Table. 1 Demographics of participants, n (%)			
	Overall n=126	Objective Warmth n=110	No Objective Warmth n=16
Mean Age (SD) (years)	55.44 (15.75)	56.15 (16.00)	50.53 (13.29)
Race	n (%)		
American Indian or Alaska Native	2 (1.59)	2 (1.82)	0 (0.00)
Black or African American	6 (4.76)	5 (4.55)	1 (6.25)
White	109 (86.51)	97 (88.18)	12 (75.00)
Multiple Races	5 (3.97)	3 (2.73)	2 (12.50)
Declined to Answer	4 (3.17)	3 (2.73)	1 (6.25)
Ethnicity			
Hispanic, Latino, or Spanish Origin	5 (3.97)	4 (3.64)	1 (6.25)
Gender			
Female	46 (36.51)	37 (33.64)	9 (56.25)
Male	80 (63.49)	73 (66.36)	7 (43.75)
Disposition			
Discharge	71 (56.35)	61 (55.45)	10 (62.50)
Admit	55 (43.65)	49 (44.55)	6 (37.50)
Patient-reported warmth	98 (77.78)	86 (78.18)	12 (75.00)
Warmth documented in HPI	7 (5.56)	7 (6.36)	0 (0.00)
Warmth documented in Physical Exam	65 (51.59)	58 (52.73)	7 (43.75)

Table 2. Comparing the average affected skin temperature (Tavg affected) of cellulitis cases when warmth was mentioned and not mentioned in the patient report, history of present illness (HPI), and physical exam

Source	Tavg affected (°C) when warmth was mentioned (95% Confidence Interval) [n]	Tavg affected (°C) when warmth was not mentioned (95% Confidence Interval) [n]	Difference (95% Confidence Interval) (p value)
Patient-reported	31.70 (31.22 – 32.19) [98]	31.03 (30.14 – 31.91) [28]	0.67 (-0.34 to 1.68) (p = 0.19)
HPI	32.16 (30.89 – 33.42) [7]	31.52 (31.07 – 31.99) [119]	0.64 (-1.20 to 2.49) (p = 0.49)
Physical exam	32.10 (31.63 – 32.56) [65]	30.98 (30.27 – 31.68) [61]	1.11 (0.29 to 1.94) (p = 0.0083)

Chapter 3

Validation of Skin Surface Temperature Measurement to Differentiate Cellulitis from Pseudocellulitis in the Emergency Department

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BACKGROUND

Infections have been identified as one of the 'Big Three' conditions that account for most of the morbidity and mortality attributable to diagnostic error.[45,46] Skin and soft tissue infections, among which cellulitis is the most common, account for ~3% of all emergency department (ED) encounters (>3 million annual visits).[5,47] Cellulitis is largely a clinical diagnosis, defined by expanding redness, warmth, tenderness and edema. Unfortunately, these characteristics are non-specific and commonly found in other inflammatory dermatologic conditions which can mimic cellulitis, such as venous stasis dermatitis, deep venous thrombosis, drug eruptions, lymphedema, and gout.[48] Collectively, these mimics of cellulitis are referred to as pseudocellulitis. A recently published report found that 30% of patients diagnosed with cellulitis in the ED actually have non-infectious mimics termed pseudocellulitis. These diagnostic errors represent a public health and patient safety risk related to unnecessary antibiotic prescribing (e.g. bacterial resistance, serious adverse drug events) and are estimated to generate $515 million in avoidable healthcare expenditures annually.[49–52]

Given the high rate of cellulitis misdiagnosis, there is an urgent need to develop strategies to improve diagnostic accuracy.[49] Skin surface temperate measurement using thermal imaging cameras has been proposed as a novel diagnostic adjunct to assist clinicians differentiate cellulitis from pseudocellulitis. However, the available studies examining this technology in a limited population of patients, specifically those diagnosed with cellulitis by the ED provider. This does not reflect the true, undifferentiated population in which cellulitis is considered as part of the differential diagnosis. Also, these studies involved small sample sizes, yielding wide confidence intervals for diagnostic performance characteristics.[53,54] As skin surface temperature differences between cellulitis and pseudocellulitis require additional validation, our primary

objective was to compare these values in a large cohort of undifferentiated, potential cellulitis cases presenting to the ED. Our secondary objective was to identify the optimal temperature measure and associated cut point for differentiating cellulitis from pseudocellulitis. We hypothesized that all skin surface temperature measures would be significantly higher for cellulitis as compared to pseudocellulitis.

METHODS

Selection criteria

This study was reviewed and approved by the local Institutional Review Board. Patients 18 years and older presenting to the ED with a chief complaint related to a visibly erythematous lower extremity were prospectively enrolled upon written consent at a quaternary care center in the Midwest. Patients were excluded if they were non-English speaking, a known prisoner, pregnant or had impaired decision making. In addition, patients with any of the following were excluded: complaint was due to an acute traumatic injury (within 5 days); complaint was in an area of past surgical procedure (within 4 weeks); implant or hardware at site of complaint, animal or human bite is cause of complaint, or complaint was exclusive to the toe(s). Emergency department research coordinators screened patients from October 2018 through March 2020 during the hours of 8am to 10pm, 7 days a week.

Data collection and chart review protocol

During the ED encounter, high resolution photograph(s) and a surface temperature image of both the participant's affected and unaffected lower extremities were obtained by the same study team member. Surface skin temperature images were taken with a FLIR One thermal camera (Generation One, FLIR Systems) attached to an iPad from a distance of ~30 cm). This camera measures surface temperatures ranging from -20°C to 120°C without direct contact and

detects temperature differences as small as 0.1°C.[54] Using the FLIR software, affected areas of skin and corresponding unaffected skin on the contralateral leg were selected within the images to generate a maximum and average temperature of the affected and unaffected legs (Figure 1). In patients with bilateral affected lower extremity skin, skin surface temperature of the ipsilateral proximal upper extremity was utilized to generate unaffected values.

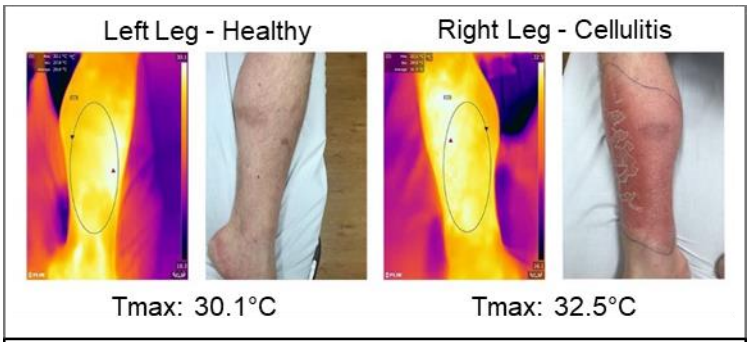

Figure 1. Example of Photographs and Corresponding Surface Thermal Images

We recorded baseline participant demographics both from patient self-report and medical chart review. We recorded participant age, biological sex, race (American Indian/Alaska Native, Asian, black or African American, Native Hawaiian or Pacific Islander, white, multiple races or declined to answer), ethnicity (LatinX yes/no). We collected information about the ED encounter including diagnostic testing (laboratory studies, imaging) and disposition.

The in-depth chart review component of the study was completed by trained abstractors. Prior to beginning chart review, all abstracted variables were clearly defined and their definitions were documented in a study codebook. Data abstraction forms were setup using REDCap software, and research coordinators, who were blinded to the study's hypothesis, were trained on the first 20 charts to ensure consistent data abstraction. Abstraction performance was monitored by double-abstracting 15% of charts (randomly selected) and checking for consistency in responses. Routine check-in meetings and frequent email communication were utilized to clarify

questions about specific patients. Emergency provider final diagnosis (cellulitis yes/no) was double abstracted for all participants. We classified the emergency provider diagnosis as cellulitis if any of the diagnosis codes associated with the ED visit were cellulitis or if the patient received antibiotic therapy for cellulitis

Expert review protocol

All encounters were independently reviewed by an expert panel of six board certified physicians to determine the gold standard diagnosis (cellulitis yes/no). The expert panel was allowed to view the clinical note (except medical decision making, diagnosis and treatment), photographs, laboratory/imaging results and surface temperature data prior to making a diagnoses. The expert panel was composed of physicians with at least 5 years of clinical experience in acute care, including two emergency medicine (EM) physicians, two infectious disease (ID) physicians, and two dermatologists (Derm). A consensus was reached when a majority of physicians agreed upon a cellulitis diagnosis. There were 17 cases where there was no consensus among the expert panel. The expert panel independently re-reviewed these 17 cases which resulted in consensus for 14 cases. For the remaining three cases, we used the treating emergency physician diagnosis as the gold standard diagnosis.

Statistical analysis

We compared differences in socio-demographic and clinical encounter variables between patients that had cellulitis and pseudocellulitis. Differences across categorical variables were compared using chi-square tests. We calculated and overall misdiagnosis rate by comparing the expert panel diagnosis with the treating emergency physician diagnosis. We calculated the difference in maximum skin temperature and 95% confidence intervals (CIS) between the

affected and healthy legs of the same participant using a two-sided paired t test and between groups using a two sided t test. Analyses were done in STATA (Stata/SE 16.1).

We used logistic regression and the associated area under the ROC curve (*C*-index) to identify which of the six skin surface temperature characteristics (maximum temperature affected, maximum temperature unaffected, average temperature affected, average temperature unaffected, maximum temperature gradient or average temperature gradient), had greatest ability to discriminate between cases of cellulitis and pseudocellulitis. We studied the characteristics having sufficient ability ($C > 0.70$) further to identify an optimal cutpoint. This was done by repeatedly and randomly splitting the full data set into 'training' and 'validation' sets in a 2:1 ratio. Randomization was constrained so training and validation sets each maintained the same fraction of cellulitis / pseudocellulitis cases as the original (full) data set. A cutpoint within the training set was found such that sensitivity would be ≥ 0.90 and specificity maximized subject to this restriction. This cutpoint was then evaluated using data from the validation set to produce honest estimates of sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV). The process was repeated 500 times for each candidate variable to produce a distribution of cutpoints and honest estimates of performance. Analyses were performed using R (ver. 4.0.3) and the associated *OptimalCutpoints* package.

RESULTS

We enrolled 204 participants in this study, and the expert panel determined that 45% (92) of participants had cellulitis (Table 1). Participants in the sample had an average age of 56.6 years, 59.3% were male and 88.2% of participants self-identified as white. There were no differences in the demographic variables between the cellulitis and pseudocellulitis groups. Overall, 59.3% of participants were discharged (52.2% in cellulitis group and 65.2% in

pseudocellulitis group; p = 0.60). The ED attending diagnosis agreed with the expert panel diagnosis in 97.8% of cases determined to be cellulitis and in 57.1% of cases determined to be pseudocellulitis (p <0.001). This corresponds to an overall misdiagnosis rate of 24.5% (50/204) and a misdiagnosis rate for cellulitis by ED attendings of 34.8% (48/138).

Table 1. Demographic and clinical encounter characteristics overall and by group, n (%)

	Overall (n=204)	Expert Panel Diagnosis		
		Cellulitis (n=92)	Pseudocellulitis (n=112)	P-Value*
Average Age (sd)	56.6 (16.5)	55.6 (15.0)	57.4 (17.78)	0.427
Male	121 (59.3%)	59 (64.1%)	62 (55.4%)	0.204
LatinX ethnicity	6 (2.9%)	3 (3.3%)	3 (2.7%)	0.807
Race				0.587
American Indian or Alaska Native	2 (1.0%)	2 (2.2%)	0 (0%)	
Asian	0 (0%)	0 (0%)	0 (0%)	
Black or African American	11 (5.4%)	4 (4.4%)	7 (6.3%)	
Multiple Races	7 (3.4%)	3 (3.4%)	4 (3.6%)	
Native Hawaiian or Pacific Islander	0 (0%)	0 (0%)	0 (0%)	
White	180 (88.2%)	81 (88%)	99 (88.4%)	
Declined to Answer	4 (2%)	2 (2.2%)	2 (1.8%)	
Disposition				0.060
Admitted	83 (40.7%)	44 (47.8%)	39 (34.8%)	
Discharged	121 (59.3%)	48 (52.2%)	73 (65.2%)	
ED Attending Diagnosis				<0.001
Cellulitis	138 (67.7%)	90 (97.8%)	48 (42.9%)	
Pseudocellulitis	66 (32.4%)	2 (2.2%)	64 (57.1%)	

* Measuring mean differences or differences in proportion between cellulitis and pseudocellulitis group

Tables 2 and 3 summarize the average and maximum skin surface temperatures respectively, including associated between limb temperature gradients, for participants with cellulitis and pseudocellulitis. Participants diagnosed with cellulitis by the expert panel had statistically significantly elevated average and maximum temperatures of their affected skin as compared to those with pseudocellulitis. Participants with cellulitis also had a statistically

significant increase in temperature gradients between their affected skin and unaffected skin as compared to those with pseudocellulitis.

Table 2. Average skin surface temperatures (°C) in participants with cellulitis and pseudocellulitis (n=204)

	Affected Skin Average Temperature	Unaffected Skin Average Temperature	Difference, Mean (95% CI), P-Value
Cellulitis, mean (95% CI)	31.9 (31.5 to 32.4)	28.7 (28.1 to 29.3)	3.2 (2.7 to 3.7), p <0.001
Pseudocellulitis (95% CI)	29.7 (29.2 to 30.3)	29.0 (28.5 to 29.5)	0.71 (0.25 to 1.2), p = 0.003
Difference, mean (95% CI), P-Value	2.2 (1.4 to 3.0), p <0.001	-0.31 (-1.1 to 0.48), p = 0.444	2.51 (1.8 to 3.2), p < 0.001
Abbreviation: CI, Confidence Interval			

Table 3. Maximum skin surface temperatures (°C) for cellulitis and pseudocellulitis (n=204)

	Affected Skin Max Temperature	Unaffected Skin Max Temperature	Difference, Mean (95% CI), P-Value
Cellulitis, mean (95% CI)	33.2 (32.8 to 33.6)	30.3 (29.7 to 30.8)	2.9 (2.5 to 3.4), p < 0.001
Pseudocellulitis (95% CI)	31.2 (30.7 to 31.7)	30.3 (29.8 to 30.9)	0.87 (0.47 to 1.3) p, 0.001
Difference, mean (95% CI), P-Value	2.0 (1.3 to 2.7), p < 0.001	-0.06 (-0.81 to 0.68), p = 0.867	2.1 (1.47 to 2.7) p <0.001
Abbreviation: CI, Confidence Interval			

Summary information (mean & standard deviation [SD]) involving recorded temperature appears in Table 4, together with the area under the ROC curve (*C*-index). Maximum and average temperature for *unaffected* areas have virtually no ability to discriminate between the two groups with C- index values of 0.517 and 0.530 respectively, and were not considered for determination of an optimal cutpoint. The other four variables (both gradient measures, maximum temperature, and average temperatures for the affected area) each had $C > 0.70$ and were explored in more detail.

Table 4. Summary information of the six skin surface temperature characteristics considered in development of an optimal cutpoint (n=204)

		Cellulitis (n = 92); mean (SD)	Pseudocellulitis (n=112); mean (SD)	C-index (95% CI)
Maximum Temperature °C				
	Affected	33.2 2.0)	31.2 (2.8)	0.715 (0.648, 0.776)
	Unaffected	30.3 (2.7)	30.3 (2.7)	0.517 (0.444, 0.585)
Average Temperature °C				
	Affected	31.9 (2.3)	29.7 (3.1)	0.706 (0.638, 0.767)
	Unaffected	28.7 (2.8)	29.0 (2.8)	0.530 (0.458, 0.599)
Temperature Gradient °C				
	for Maximum	2.95 (2.3)	0.87 (2.1)	0.740 (0.674, 0.799)
	for Average	3.22 (2.7)	0.71 (2.5)	0.751 (0.685, 0.808)
Abbreviation: CI, Confidence Interval				

Each training set involved random samples of n = 136 records (66.7% of overall sample), each containing 61 (44.9%) cellulitis cases and 75 pseudocellulitis cases; the remaining 68 records held 31 (45.6%) cases of cellulitis (and 37 cases of pseudocellulitis) and constituted a validation set. This process of splitting the data into training and validation sets was repeated 500 times. Table 5 shows the most frequently occurring cutpoint observed in the training set, along with the operating characteristics when that same cutpoint is applied to the validation set. The maximum temperature cutpoint was 31.2°C in the affected skin and this corresponded with a mean negative predictive value of 0.935 (SD, 0.047) and a mean sensitivity of 0.968 (SD, 0.023). NPV and sensitivity were better in the maximum temperature cutpoint than in any other temperature characteristics that were evaluated. Application of this cutoff to our validation cohort would have resulted in a 24% (12/50) relative reduction in overdiagnosis.

Table 5. Cutpoints and corresponding operating characteristics when cutpoint is applied to validation set

	Maximum Temperature (affected)	Average Temperature (affected)	Temperature Gradient (for Maximum)	Temperature Gradient (for Average)
Cutpoint	≥ 31.2 °C	≥ 29.25 °C	≥ 0.40 °C	≥ 0.20 °C
% chosen in 500 repetitions	34.2%	40.8%	22.0%	18.6%

Sensitivity					
	Range	0.935-1	0.871-1	0.871-0.903	0.903-0.903
	Mean (SD)	0.968 (0.023)	0.952 (0.028)	0.901 (0.008)	0.903 (-)
Specificity					
	Range	0.243-0.541	0.243- 0.595	0.216- 0.568	0.243-0.568
	Mean (SD)	0.388 (0.067)	0.404 (0.065)	0.387 (0.067)	0.350 (0.068)
Negative Predictive Value					
	Range	0.818-1	0.769 -1	0.727-0.875	0.750 -0.875
	Mean (SD)	0.935 (0.047)	0.909 (0.504)	0.821 (0.027)	0.808 (0.029)
Positive Predictive Value					
	Range	0.509- 0.656	0.509-0.660	0.491-0.636	0.500-0.636
	Mean (SD)	0.571 (0.028)	0.573 (0.029)	0.553 (0.027)	0.539 (0.027)

DISCUSSION

Our results represent the largest validation study (n=204) to date of skin surface temperature variables in a cohort of ED patients with potential cellulitis. The expert panel consensus indicated that the ED attending overdiagnosed cellulitis in 35% of cases, consistent with what has been observed in other studies,[49,55] This study adds to the previous literature which utilized smaller sample sizes and limiting inclusion to only patients with an emergency provider assigned diagnosis of cellulitis. Our approach was pragmatic in that all patients presenting to the ED with potential cellulitis, acute leg complaint involving visible erythema, were included. This eliminates inter-provider diagnostic variability and more accurately reflects the population this diagnostic aide would be applied to in clinical practice.

Consistent with the existing literature, we observed that the maximum and average affected surface skin temperature in participants with cellulitis is significantly higher than in patients with pseudocellulitis and this is true for the differences in temperature gradient as well.[28] However, while the Ko et al. study used temperature gradient to develop a cutpoint[28], our analysis found maximum temperature of the affected skin to be the temperature characteristic that optimizes sensitivity and negative predictive value for cellulitis.

The presence of a significant differences in both absolute temperatures and affected/unaffected limb gradients between cases of cellulitis and pseudocellulitis supports that thermal imaging has the potential for use as a diagnostic adjunct that can help differentiate these conditions. Our large dataset enabled comparing the diagnostic performance of the different thermal variables and derivation of cutpoints. Application of a diagnostic aide with a high negative predictive value would be particularly helpful in the ED setting where systems factors such as time pressures, incomplete information, and increased cognitive load compound the challenges of diagnostic uncertainty.

As with any new diagnostic technology, barriers to implementation must be considered. While surface thermal imaging devices could be easily deployed at the bedside due to models and software that is designed to integrate with portable electronic devices (e.g. iPhone), the fact remains that currently no emergency providers have access to these devices. An additional concern is clinical uptake: will providers decide to use these devices and then act on the results. Results from a trial of procalcitonin, another diagnostic aide aimed at reducing non-indicated antibiotic prescribing, suggests that clinicians may simple ignore the results despite established performance efficacy and educational efforts. Additionally, it will be necessary to consider who will acquire the images (e.g. registered nurse, emergency technician) and process temperature values in the software, and what type of training will be required.

Limitations

This study has a few limitations. First, this was a single center study with a predominantly white population. There is need for further validation of this technology in larger, more diverse patient populations.

Conclusions

Cellulitis results in skin surface temperature elevations significantly greater than pseudocellulitis. Surface thermal imaging may represent a useful adjunct to the clinical assessment of cellulitis (reduce misdiagnosis) but additional validation of diagnostic performance and cutoff values needed. Antibiotic misuse related to diagnostic uncertainty and error remains a significant public health and individual patient safety concern. Efforts to develop diagnostic tools that address these primary, yet understudied, drivers of suboptimal antibiotic utilization. Future work will focus on evaluating if ED attendings use this in diagnostic decision making, and to validate this work in vulnerable subgroup populations such as older adults.

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