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Diagnosis and treatment of the invasive extension of bacteria (cellulitis) from chronic wounds utilising point-of-care fluorescence imaging

Charles A. Andersen | **Katherine McLeod** | **Rowena Steffan**

Vascular/Endovascular/Limb Preservation Surgery Service, Madigan Army Medical Center, Joint Base Lewis-McChord, Washington, USA

Correspondence
Charles A. Andersen, MD, FACS, MAPWCA, Vascular/Endovascular/Limb Preservation Surgery Service, Madigan Army Medical Center, 9040A, Joint Base Lewis-McChord, Washington, USA.
Email: charles.a.andersen.civ@mail.mil

Abstract

Early diagnosis of wound-related cellulitis is challenging as many classical signs and symptoms of infection (erythema, pain, tenderness, or fever) may be absent. In addition, other conditions (ie, chronic stasis dermatitis) may present with similar clinical findings. Point-of-care fluorescence imaging detects elevated bacterial burden in and around wounds with high sensitivity. This prospective observational study examined the impact of incorporating fluorescence imaging into standard care for diagnosis and management of wound-related cellulitis. Two hundred thirty-six patients visiting an outpatient wound care centre between January 2020 and April 2021 were included in this study. Patients underwent routine fluorescence scans for bacteria (range: 1-48 scans/patient). Wound-related cellulitis was diagnosed in 6.4% (15/236) of patients. In these patients, fluorescence scans showed an irregular pattern of red (bacterial) fluorescence extending beyond the wound bed and periwound that could not be removed through cleansing or debridement, indicating the invasive extension of bacteria (wound-related cellulitis). Point-of-care identification facilitated rapid initiation of treatments (source control and antibiotics, when warranted) that resolved the fluorescence. No patients had worsening of cellulitis requiring intravenous antibiotics and/or hospitalisation. These findings demonstrate the utility of point-of-care fluorescence imaging for efficient detection and proactive, targeted management of wound-related cellulitis.

KEYWORDS

cellulitis, fluorescence imaging, infection, MolecuLight, wounds

Key Messages

- efficient, accurate diagnosis of cellulitis is critical to avoid costly complications
- a unique pattern of red fluorescence extending beyond the wound was observed in all cases of wound-related cellulitis

- imaging aided in the early diagnosis of wound-related cellulitis, resulting in the initiation of oral antibiotics without delay, avoiding progressive cellulitis requiring intravenous antibiotics or hospitalisation.

1 | INTRODUCTION

Cellulitis is an acute inflammatory condition of the dermis and subcutaneous tissue caused by bacterial entry into the dermis. Cellulitis can originate from chronic wounds or acute trauma through an invasive extension of bacteria, most commonly *S. aureus*, into the adjacent dermis or subcutaneous tissue resulting in breakdown of the skin or skin damage (eg, bite or a wound).[1,2] This has been referred to as "limited" or wound-related cellulitis.[3] Chronic venous insufficiency, peripheral vascular disease, lymphoedema and comorbidities that result in immunosuppression (ie, diabetes) are all risk factors for development of wound-related cellulitis.[4] These are also risk factors for wounds and key contributors for wound chronicity.[5] As open wounds present an entry point for bacteria, clinicians specialising in wound care are on constant alert for any symptoms of this dangerous and challenging to diagnose clinical conundrum.

Cellulitis accounts for 10% of all infectious disease-related US hospitalizations.[6] In 2015, US hospitals charged $3.7 billion for cellulitis (both with and without major complications), with an average charge per cellulitis admission of $26 534.[7] Patients with potential cellulitis typically present to primary care or hospital outpatient departments including the emergency department[8] and, in the event of wound-related cellulitis, to wound clinics. Because of the severity of this infection, antibiotics are typically used to manage cellulitis and are quickly prescribed in the emergency department setting when "red leg syndrome" presents, with substantial variation in the type of antibiotic regimens used.[9] Antibiotics are needed to manage the infection because if left untreated, cellulitis can lead to more serious complications including bacteraemia, necrotizing fasciitis, endocarditis, or shock.[2,7] Severe cellulitis in patients with other comorbid conditions may result in death. Clinicians therefore have critical decisions to make—and need to diagnose cellulitis accurately and as soon as possible to avoid these serious consequences. Currently, no gold standard diagnostic techniques exist to aid in the diagnosis of cellulitis. As such, misdiagnosis can occur in up to one-third of patients,[10-12] with costly clinical and economic consequences. Among patients misdiagnosed with cellulitis, 85% experience avoidable hospital admission and 92% receive unnecessary antibiotics.[12] Misdiagnosis may contribute to the use of antibiotics that could lead to antibiotic resistance as well as an increased risk of complications (eg, renal damage or renal insufficiency, septic shock) resulting from inappropriate treatment.[13] Improved methods of diagnosing cellulitis are essential to mitigate these outcomes.

Diagnosis of wound-related cellulitis is most commonly made by examining medical history and assessment of the affected skin area.[14] When cellulitis is associated with a wound, it is typically identified by classic signs and symptoms of infection including warmth, oedema, tenderness, erythematic tissue around the wound, and in some cases, pain.[3,7] However, these symptoms are also common among other lower extremity conditions including venous stasis dermatitis,[15] making diagnosis of wound-related cellulitis a substantial challenge. Additional diagnostics including biochemical tests and imaging (ie, computerised tomography scans) are available but are not widely used because of inconsistent results and the presence of confounding factors (eg, diabetes) that may make interpretation of results challenging.[8]Point-of-care fluorescence imaging for detection of elevated bacterial load (MolecuLight *i:X*, MolecuLight, Toronto, ON, Canada) presents an intriguing opportunity to reduce misdiagnosis of cellulitis and enable more proactive, earlier treatment. This handheld imaging technology uses safe violet light to detect problematic levels of surface and subsurface bacterial burden (at loads $>10^4$ CFU/g) in and around wounds.[16,17] Red or cyan fluorescence signals on images are indicative of the presence of harmful levels of bacteria and have a positive predictive value between 93% and 100%.[16-19] *Staphylococcus aureus*, a common pathogen contributing to wound-related cellulitis,[20] is among more than 28 pathogens that produce red fluorescence when illuminated by the violet light of the device.[21,22] Clinical studies have demonstrated the diagnostic sensitivity of fluorescence imaging to be 300% to 400% greater than the current standard of care assessment of clinical signs and symptoms for detecting the presence of elevated bacterial loads ($>10^4$ CFU/g) in the wound and immediate periwound tissue.[16,23] However, potential bacteria within surrounding intact skin were not evaluated in those trials. The detection depth capability of this imaging procedure ($\sim$1.5 mm[24]) suggests that epidermal and dermal bacterial infections may be detectable. A compelling case of this technology being used to detect acute cellulitis radiating from a wound has been reported in the literature,[25]

but further investigation is warranted. In this prospective observational clinical study, we evaluate the impact of fluorescence imaging for detection of elevated bacterial loads on the diagnosis and management of wound-related cellulitis.

2 | MATERIALS AND METHODS

2.1 | Patients and study design

Patients 18 years or older with a wound that presented to the hospital outpatient wound clinic at the Wound Care Limb Preservation Clinic at Madigan Army Medical Center between January 2020 and April 2021 were considered eligible to participate in this observational prospective study, and none were excluded. Over a 16-month period, we critically assessed the fluorescence scans of 236 patients, together with their clinical signs and symptoms, looking for patterns in the fluorescence scans that might aid in various diagnoses, including wound-related cellulitis. Wound types evaluated included diabetic foot ulcers (DFUs), venous leg ulcers (VLUs), pressure ulcers (PU), surgical sites, and trauma wounds. All patients underwent routine standard of care assessment, which included a review of patient history and evaluation of clinical signs and symptoms of infection (eg, erythema, warmth, pain). Fluorescence scanning was performed by the clinical team and repeated iteratively after cleansing or debridement, as needed.[26] The fluorescence scans were acquired per the intended use of the device, which is part of our routine care. Therefore, no formal written informed consent was required from patients. Patient information was de-identified and anonymised, as such, ethics approval was not required for this non-interventional study.

2.2 | Fluorescence imaging procedure

The fluorescence imaging (MolecuLight *i*:X, MolecuLight, Toronto, Canada) procedure was performed by the clinical team if deemed medically necessary.[26] The imaging procedure uses safe, violet (405 nm) light to detect bacteria at the point-of-care.[16,17] When illuminated with this violet light, bacteria at loads of $>10^4$ CFU/g produce a red or cyan fluorescence signal, enabling identification of the extent and location of bacterial burden in the wound.[16-18,21] The clinical team received extensive didactic and hands-on training in fluorescence scanning and image interpretation[24] and had completed an online image interpretation training module to enhance accurate interpretation of scans and receive certification. Prior to fluorescence imaging, the patient's wound was positioned parallel to the imaging device prior to capturing the scan. After scanning the wound with the imaging device, the physician then reviewed the fluorescence scans at the point-of-care for presence of red or cyan in images, indicative of bacteria at loads $>10^4$ CFU/g.

The diagnosis of cellulitis was based on patient history, assessment of clinical signs and symptoms, and presence of red fluorescence extending in a fan-like distribution beyond the wound or wound margins that could not be removed with aggressive cleansing and debridement. Patients who were diagnosed with wound-related cellulitis underwent fluorescence-guided wound debridement, as needed, and were started on antibiotics. Images were captured at weekly follow-up to assess the resolution of the cellulitis.

3 | RESULTS AND DISCUSSION

3.1 | Patient characteristics

Over the 16-month study, 236 patients were evaluated as per standard of care, and fluorescence scans were captured to assess for various wound-related complications, including cellulitis. Wound-related cellulitis was diagnosed in 15 of 236 patients assessed (range of 1-48 scans for each patient). Patients with wound-related cellulitis ranged in age from 23 to 87 years, the average age of patients was 62.8 years (Table 1). Most patients diagnosed with wound-related cellulitis were male (71.4%). The incidence of wound-related cellulitis was comparable between chronic wounds (eg, VLU, DFU, PU) and acute wounds (eg, trauma wound, surgical site, blisters caused by oedema). Other wound types assessed included wounds resulting from cancer treatments (2), perianal fistula (1), and occipital keloid (1).

A fluorescence scan was performed based on medical necessity to aid knowledge of bacteria location at levels requiring treatment, as previously described by Oropallo et al.[26] Briefly, these criteria included presence of comorbidities (eg, history of wound infection, non-healing wounds), presence of clinical signs and symptoms of infection (eg, erythema), indication of bacteria on previous fluorescence scan, or as part of baseline wound assessment. After capturing a fluorescence scan, images were reviewed to identify patterns of fluorescence indicative of bacteria at loads $>10^4$ CFU/g. In reviewing fluorescence patterns on images, three categories of bacterial distribution within and outside of the wound bed emerged:

1. *Surface bacteria*. Fluorescence signal that extended outside the wound bed and could be removed through vigorous cleaning using dilute sodium hypochlorite

TABLE 1 Characteristics of the 15 of 236 patients diagnosed with wound-related cellulitis

	N (%)		N (%)
Average age (years)	62.8	Male (%)	10 (71.4)
		Female (%)	5 (35.7)
Wound Types			
Venous Leg ulcer	3 (21.4)	Trauma wound	1 (7.1)
Diabetic Foot Ulcer	2 (14.3)	Surgical site	2 (14.3)
Pressure injury	2 (14.3)	Oedema Blisters	1 (7.1)
		Other	4 (28.6)

solution or debridement was not diagnosed as wound-related cellulitis. Notably, the cyan fluorescence from *Pseudomonas*, a surface pathogen, could typically be removed in this manner, in addition to the red signals of other bacteria.[21]

2. *Bacteria limited to wound or callus tissue*. In wounds with a callus present, red or cyan fluorescence from bacteria often extended deep into the tissue and frequently persisted after aggressive, sharp debridement to remove the callus. This was especially common among DFUs. Red fluorescence from bacteria was usually blush red or orange in hue because of its subsurface nature.[24] Fluorescence was confined to the ring of callus tissue and thus was not diagnosed as wound-related cellulitis.

3. *Invasive extension of bacteria, beyond the wound bed and periwound with irregular patterns of red fluorescence*. This pattern of fluorescence could not be removed with vigorous scrubbing with a cleanser, warranting critical evaluation for cellulitis. This irregular pattern of red fluorescence extended beyond the margins of the wound and was not consistent with tissue landmarks. Figure 1 summarises the clinical decision algorithm for wound-related cellulitis based on clinical assessment and fluorescence scan information.

Table 2 summarises all clinical cases where wound-related cellulitis was diagnosed. Among patients diagnosed with wound-related cellulitis, clinical signs and symptoms of infection varied widely from patient to patient. Tenderness (60.0%), drainage (46.7%), and erythema (33.3.%) were the most common symptoms detected in patients diagnosed with wound-related cellulitis. No signs or symptoms of infection were observed in one patient with occipital keloids and in another with a perianal fistula. Fever was not detected in any patient at the time of diagnosis. Red fluorescence indicative of bacteria was evident in all cases where wound-related cellulitis was diagnosed. Fluorescence scans of these wounds showed a pattern of red fluorescence extending beyond the wound bed and periwound. Persistence of this red fluorescence signal after fluorescence-targeted cleaning or debridement supported diagnosis of wound-related cellulitis. Patients diagnosed with wound-related cellulitis were immediately started on topical antimicrobials and/or antibiotics. Cyan fluorescence (indicative of *Pseudomonas*) was not observed in any wounds diagnosed with wound-related cellulitis, consistent with the fact that *Pseudomonas* is not typically associated with cellulitis.[27] In patients where cyan fluorescence was observed on scan, cleaning and debridement were performed to address the *Pseudomonas*. If cyan signal persisted, a subsequent scan was performed at follow-up visit 1 week later.[26]

Real-time information on the presence and location of bacteria in and around wound tissue directed traditional strategies aimed at eliminating bacterial burden including guiding the extent and location of cleaning or debridement. The efficacy of these strategies was evaluated immediately to determine whether an additional round of cleaning or debridement was needed. Information provided by fluorescence scans also enhanced clinician confidence in prescribing antibiotics without delay. Antibiotics were initiated when fan-shaped fluorescence signals persisted after image-informed debridement or cleaning. At follow-up visits, fluorescence scans were used to track the efficacy of treatments and supported treatment planning (ie, additional debridement or continuation of antibiotics). Below we call out four specific patient examples to describe their treatment and to aid understanding of how point-of-care fluorescence imaging was incorporated into standard care to support the diagnosis and management of wound-related cellulitis.

3.2 | Example 1

A 75-year-old male with a history of type 2 diabetes, hypertension, stage 3 kidney disease, and venous stasis developed paraplegia following a cervical spine operation requiring him to be wheelchair bound. The use of a new wheelchair resulted in the development of a sacral wound. Upon initial clinical examination, the clinician noted the presence of macerated and necrotic tissue,

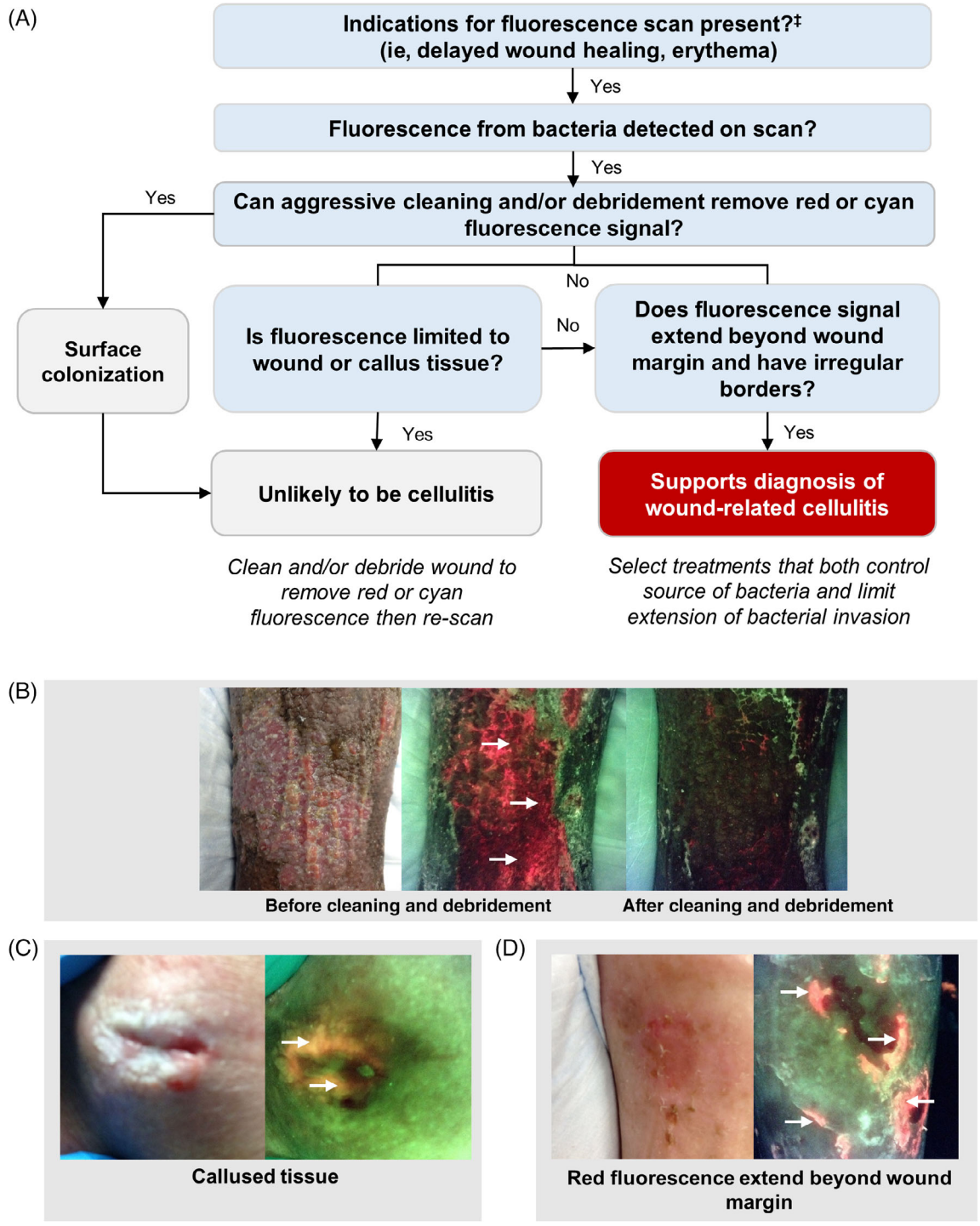

FIGURE 1 Decision tree for diagnosis of wound-related cellulitis supported by fluorescence imaging. (A) Clinical decision tree incorporating fluorescence imaging information to identify wounds with bacteria burden, and potential cellulitis. (B) In wounds with surface colonisation, bacterial fluorescence signal is eliminated with aggressive wound hygiene strategies. (C) Red bacterial fluorescence in callused tissue is unlikely to be wound-related cellulitis, but often appears pink or orange because of the subsurface location of bacteria below callus. (D) Bacterial fluorescence with irregular borders beyond the periwound region was indicative of wound-related cellulitis in this patient. White arrows point to regions of red fluorescence indicative of bacteria at loads $>10^4$ CFU/g. ‡Based on guidelines developed by Oropallo et al[26]

tenderness, slough, and drainage (Figure 2A). Wound-related cellulitis was not suspected based on clinical examination. However, fluorescence scans showed bright red fluorescence extending in the skin around the wound region (Figure 2B). This extensive invasion of bacteria was not reduced after cleansing the wound and surrounding area and was not exclusive to the macerated tissue, supporting the clinical diagnosis of cellulitis. Based

TABLE 2 Summary of clinical findings for the subset of patients (6.4%) diagnosed with wound-related cellulitis

	Patient details	Wound details	Clinical signs and symptoms (CSS)	Fluorescence detected?	Value of fluorescence scans
1	75 y.o. male	Sacral wound ulcer	Drainage, necrotic tissue, slough, tenderness, and warmth	Yes, red fluorescence extending beyond wound bed and periwound	Persistence of red fluorescence beyond macerated tissue supported diagnosis of wound-related cellulitis
2	87 y.o. male	Venous leg ulcer (VLU) on both lower legs	Pain, erythema on both legs	Yes, bright red fluorescence covering large area within and surrounding wound bed and periwound	Aided differentiation between stasis dermatitis and wound-related cellulitis
3	64 y.o. male	VLU	Redness in periwound region; induration	Yes, red fluorescence outside of margins of VLU, matching regions of erythema	Supported suspicion of wound-related cellulitis and decision to perform another round of debridement
4	60 y.o. male	Diabetic foot ulcer (DFU)	Necrotic tissue, slough	Yes, red fluorescence beyond wound bed in abnormal pattern	Supported clinical diagnosis, together with CSS
5	77 y.o. male	Left foot trauma	Pain, erythema around wound	Yes, red fluorescence extending beyond wound bed	Presence of pain along with persistence of red fluorescence after image-informed debridement supported decision to prescribe antibiotics
6	45 y.o. female	Right breast surgical site	Drainage, exudate, tender, erythema around wound	Yes, irregular bright red fluorescence extending beyond periwound, consistent with pattern of erythema	Red fluorescence outside of wound bed prompted cleansing. Persistence of red fluorescence after cleansing supported implementation of additional treatment
7	23 y.o. female	Transverse incision after caesarean section	Necrotic tissue, slough, and tenderness	Yes, bright red fluorescence extending outside of incision	Aided in detection of red fluorescence beyond wound bed and supported decision to initiate antibiotics
8	65 y.o. male	VLU on lower left leg	Drainage/exudate, oedema, tenderness, warmth	Yes, blush red fluorescence dispersed around wound	Helped to distinguish between trauma cause by compression wrap and bacteria involvement in that region of tissue
9	62 y.o. female	Mid back wound	Erythema, pain, increased drainage, slough	Yes, bright ring of red fluorescence around the edge of wound	Ring of red fluorescence extending well beyond irregular border around wound edge supported decision to initiate antibiotics
10	83 y.o. male	Ulcer on left heel	Tender, maceration present	Yes, red fluorescence extending beyond wound edges	Distribution of red fluorescence well beyond wound bed supported diagnosis of wound-related cellulitis
11	76 y.o. male	Bilateral lower extremity oedema blisters and ulcerations	Drainage, oedema, scattered blisters, and ulcerations	Yes, bright red fluorescence distributed around blister	Distribution of red fluorescence clearly outside of blistered wound supported diagnosis of wound-related cellulitis

(Continues)

TABLE 2 (Continued)

	Patient details	Wound details	Clinical signs and symptoms (CSS)	Fluorescence detected?	Value of fluorescence scans
12	42 y.o. female	Perianal fistula	None	Yes, red fluorescence around wound bed	Distribution of red fluorescence around seton supported diagnosis, and informed location of debridement
13	69 y.o. male	Stasis ulcer on median right ankle	Drainage/exudate, tender, and warm tissue	Yes, red fluorescence along edge of wound	Fluorescence scan information and presence of drainage supported diagnosis and decision to initiate antibiotics
14	43 y.o. male	Occipital keloid	None	Yes, bright red fluorescence dispersed throughout keloid	Images alerted clinician to presence of bacteria distributed across occipital keloid
15	71 y.o. female	Abscess near breast	Small amount of drainage, tenderness, oedema	Yes, red fluorescence beyond periwound region in erythematous region	Detection of red fluorescence in surrounding tissue that persisted after washing wound and periwound supported diagnosis of wound-related cellulitis

Abbreviations: CSS, clinical signs and symptoms; DFU, diabetic foot ulcer; VLU, venous leg ulcer; y.o., year old.

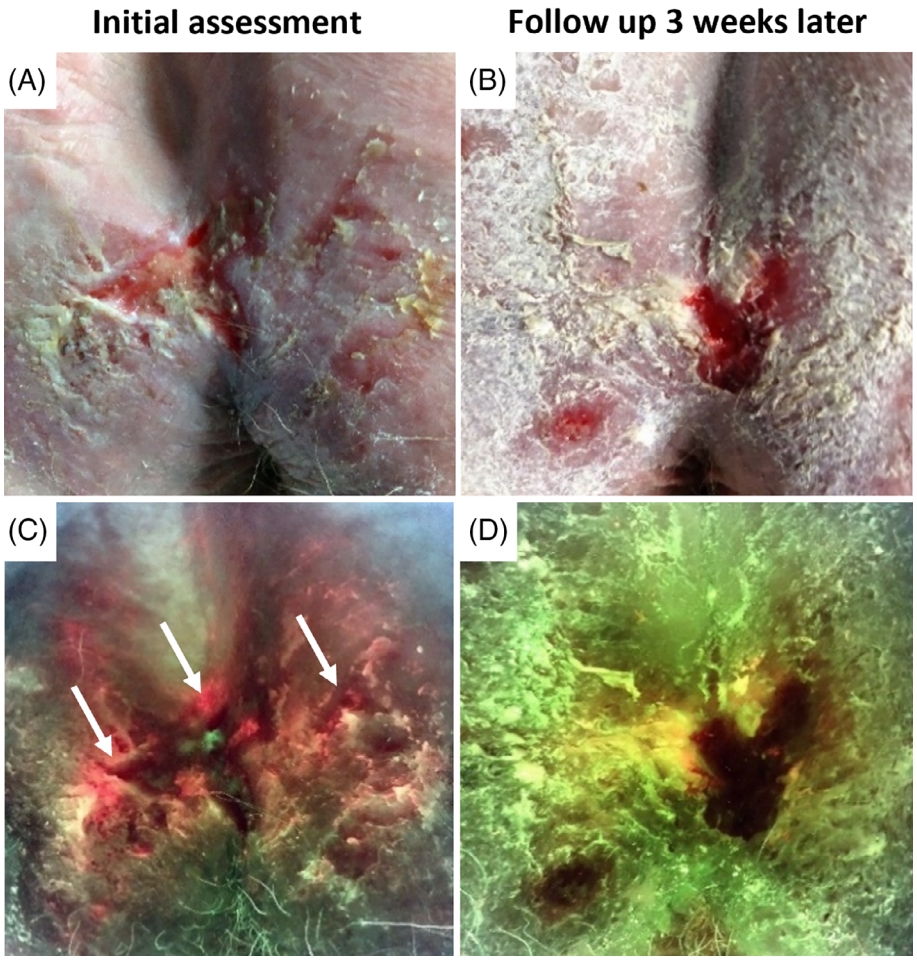

FIGURE 2 Example 1, sacral pressure ulcer. Standard (left) and fluorescence (right) scans taken at initial assessment and at follow-up 4 weeks later. (A, C) At initial assessment, fluorescence images showed bright red fluorescence (white or red arrows) indicative of elevated bacterial burden dispersed in macerated tissue and beyond periwound region. The wound underwent debridement and application of a topical antimicrobial. (B, D) At a follow-up visit 3 weeks later, a significant reduction in red fluorescence in the periwound region was observed. The wound went on to heal 6 weeks after initial assessment

on the scan information and clinical assessment, the clinician decided to initiate systemic antibiotics (Doxycycline, BID, 100 mg, 21 days) and applied a zinc spray and highly absorbent foam dressing. Over the next few weeks at each follow-up visit, a decrease in red fluorescence signal was observed. The wound continued to be routinely cleaned with sterile saline and debrided under fluorescence guidance at each visit. A topical zinc spray was then applied. At a follow-up visit 1 month after initial diagnosis, red fluorescence and wound size were substantially decreased (Figure 2C,D). The wound went on to heal 6 weeks after the initial assessment.

3.3 | Example 2

An 87-year-old male with a history of emphysema, pulmonary fibrosis, hypertension, and chronic venous insufficiency was followed in the wound clinic weekly for monitoring and treatment of recurrent bilateral VLUs because of his chronic venous insufficiency. The patient had severe chronic stasis dermatitis. He was treated weekly with topical wound management and compression wraps and was imaged, when warranted, to closely monitor bacterial status and wound progress. On a subsequent follow-up visit, the patient's ulcer remained stagnant with no obvious signs of infection, other than increased erythema. The clinical question was whether the erythema was stasis dermatitis or cellulitis. A diagnosis of cellulitis could not be made based on a clinical examination alone. However, a fluorescence scan showed bright red fluorescence, indicative of bacterial loads $>10^4$ CFU/g, spread in a large area extending beyond the wound bed (Figure 3A,D), which could not be removed with cleansing and debridement. The persistence of red fluorescence extending beyond the wound bed prompted the clinician to add antibiotics to the treatment plan (Doxycycline, BID 100 mg for 14 days). One week after

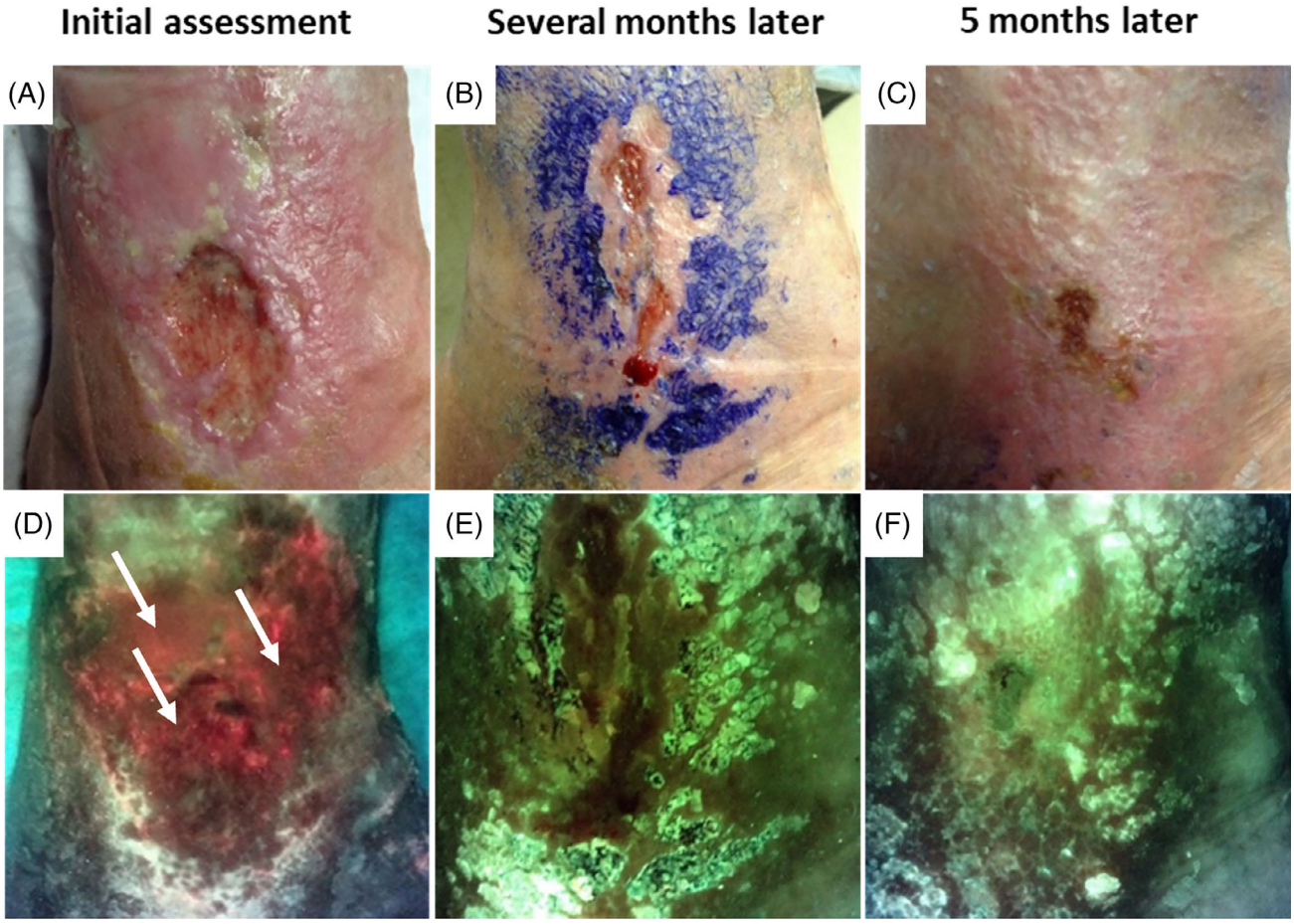

FIGURE 3 Example 2, suspected stasis dermatitis. (A, D) At initial presentation, a fluorescence scan of this recurrent venous leg ulcer showed a large region of bright red fluorescence in and around the wound bed (white arrows), indicative of elevated bacterial load. Scan and clinical information prompted initiation of antibiotics and topical antimicrobials. (B, E) At follow-up several months later, the wound was treated with gentian violet (top, centre). Fluorescence scan showed an absence of red or cyan (bacterial) fluorescence in and around the wound. (C, F) Twelve months after initial diagnosis, wound-related cellulitis was no longer observed and the wound had healed

the initiation of systemic antibiotics, there was a significant reduction in the amount of red fluorescence observed in and around the wound. On weekly follow-up, the red fluorescence resolved, and the wound healed in 1 month. The patient has developed recurrent ulcers requiring compression and had an additional episode of wound-related cellulitis requiring antibiotics.

3.4 | Example 3

A 64-year-old male with a history of pulmonary embolism and venous stasis developed a leg ulcer on his lower left extremity. He was receiving treatment for the leg ulcer for 4 months prior to visiting the wound clinic. The wound presented with tenderness, erythema, necrotic tissue, and slough (Figure 4A). Because of the significant amount of erythema around the wound, there was suspicion of cellulitis. The wound was scrubbed with dilute sodium hypochlorite and underwent sharp debridement followed by a fluorescence scan. The scan showed red fluorescence extending beyond the periwound region that was not associated with a callus or macerated tissue (Figure 4B). The scan information and clinical examination confirmed the invasive extension of bacteria, characteristic of wound-related cellulitis. The wound was treated with topical antimicrobials (wound gel and antimicrobial foam dressing) and compression. The patient also had a history of infected total joints. Based on the scan and a history of infection in his total joints, he was started on systemic antibiotics (Doxycycline 100 mg BID, 14 days). On follow-up visits, the erythema resolved and the red fluorescence decreased. On a follow-up visit 6 weeks later, wound size was significantly smaller and fluorescence scan was negative for bacterial fluorescence (Figure 4C,D). The patient continued to receive topical antimicrobials and compression, and the wound went on to heal.

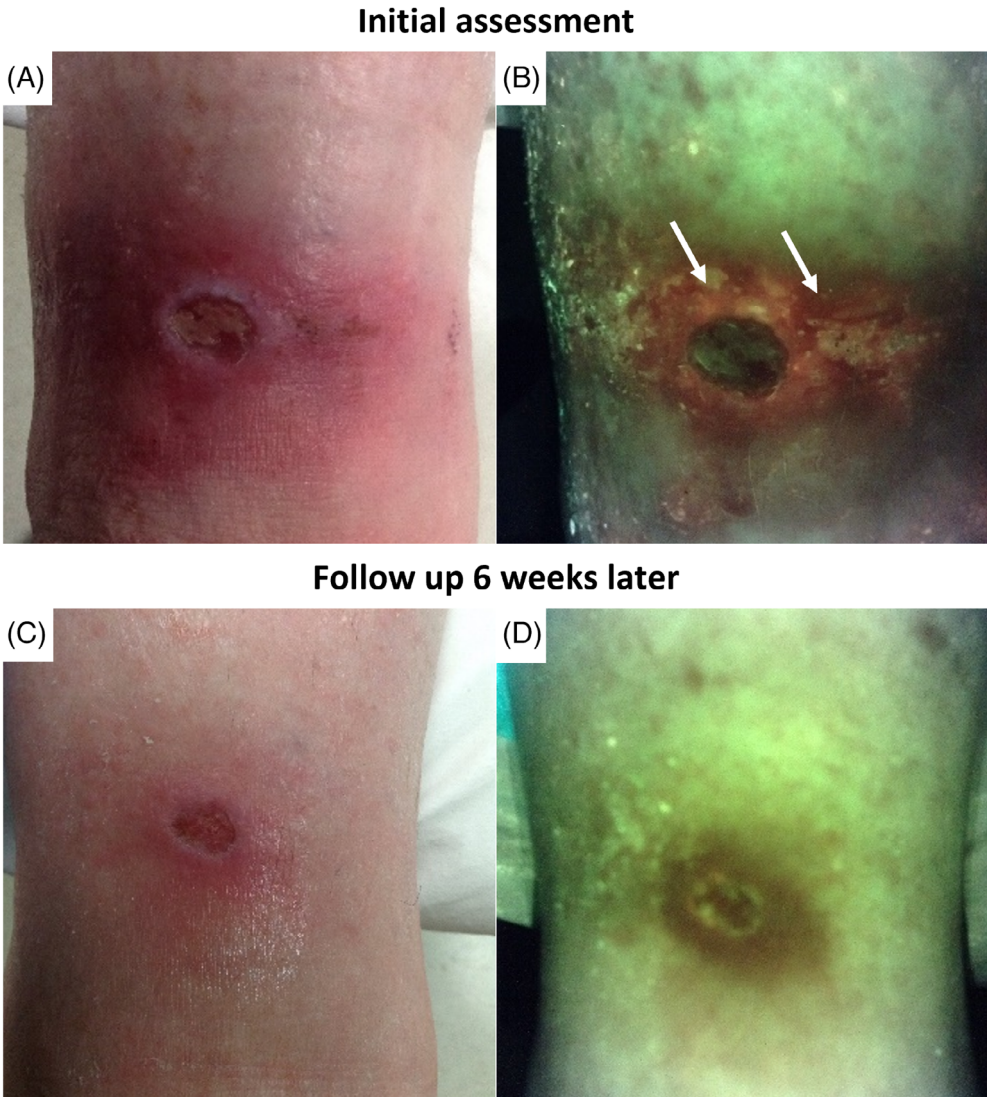

FIGURE 4 Example 3, venous leg ulcer. (A, B) At initial examination, significant erythema was observed around wound. Fluorescence scan showed bright red fluorescence indicative of elevated bacterial burden (white arrows) in erythematous region surrounding the wound, supporting diagnosis of cellulitis. Antibiotics were initiated along with application of a topical antimicrobial. (C, D) After 6 weeks, the wound size and erythema were greatly reduced. Fluorescence scan also was negative for bacterial signal indicating the efficacy of selected treatments

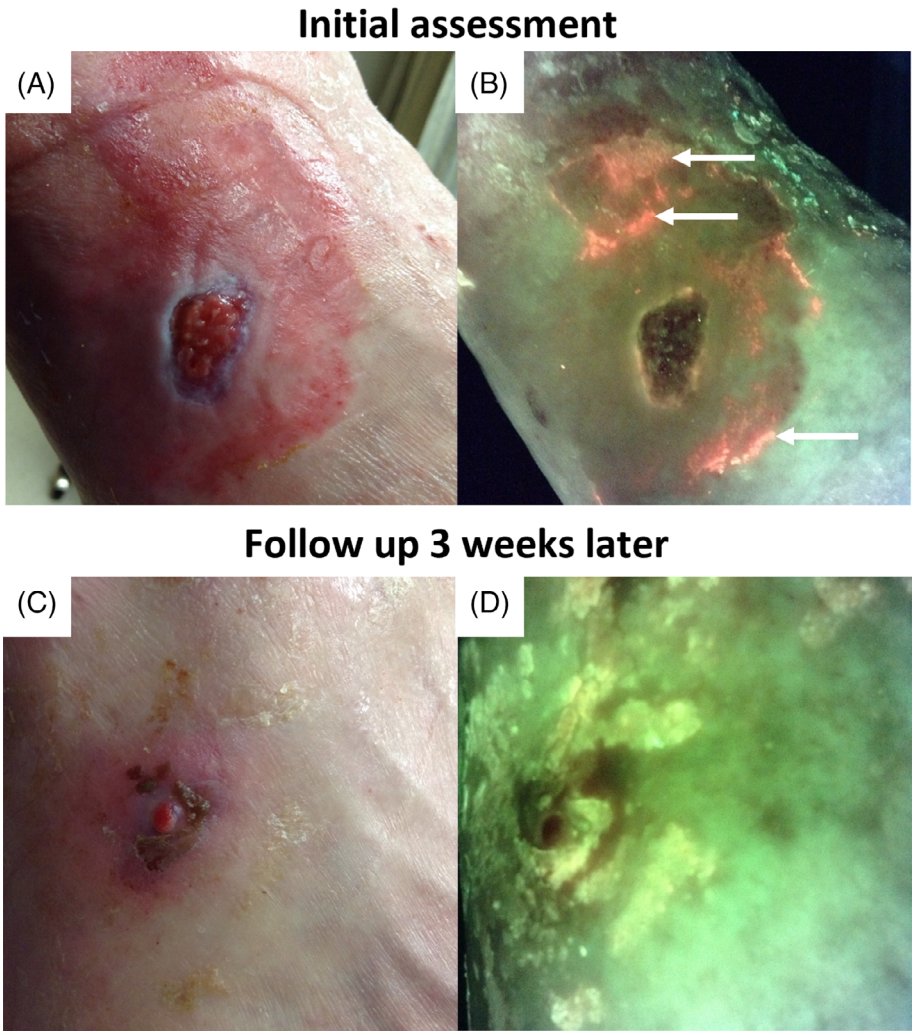

FIGURE 5 Example 4, dorsal foot ulcer. (A) Upon initial examination, strong odour and erythema were detected from the wound and surrounding region. (B) Fluorescence scan showed red fluorescence beyond the periwound region (white arrows). The wound initially underwent debridement targeted to regions of red fluorescence, but red fluorescence signal persisted prompting the clinician to include antimicrobials and compression. (C, D) Three weeks after the diagnosis of wound-related cellulitis, the wound size was significantly smaller and negative for bacterial fluorescence

3.5 | Example 4

A 60-year-old male with type 2 diabetes was previously evaluated in the ER because of increasing drainage and strong odour from a traumatic wound on the dorsum of his left foot. The patient was referred to the wound care clinic. Upon clinical examination, the wound had necrotic tissue with an odour. There was a rim of erythema around the wound (Figure 5A). The patient did not report any pain present because of his neuropathy. The wound was sharply debrided with the removal of necrotic tissue and targeted areas of red fluorescence and cleaned with dilute sodium hypochlorite solution and re-scanned. (Figure 5B). A repeat scan was performed after the debridement, demonstrating persistent red fluorescence beyond the margins of the wound. The positive scan and the clinical examination supported diagnosis of wound-related cellulitis. The wound was covered with a cadexomer-iodine gel pad and foam dressing and antibiotics were initiated. At a follow-up visit 3 weeks later, the wound was re-scanned and red fluorescence was no longer present (Figure 5C,D). Because of the negative fluorescence scan, the clinician decided to proceed with allograft placement on the dorsal foot. The wound went on to heal 1 month after the initial assessment.

4 | DISCUSSION

Cellulitis resulting from invasive extension of bacteria from wounds presents a diagnostic dilemma, especially when distinguishing between erythema from cellulitis or erythema because of inflammation and stasis dermatitis. If cellulitis is present, early identification and treatment of this invasive extension of bacteria are critical to prevent the cellulitis from progressing. This large, observational study designed to report on real-world complex wounds provided evidence that point-of-care fluorescence imaging of the presence and location of bacterial loads enhanced identification of wounds with invasive extension of bacteria, particularly in patients lacking obvious symptoms of wound-related cellulitis. Fluorescence scans

performed before, during, and after procedures aimed at removing bacterial burden (eg, debridement, cleansing),[26] or prior to prescribing antibiotics, enabled proactive wound care and provided immediate feedback on treatment efficacy that helped to (a) limit the progression of wound-related cellulitis, (b) avoid hospitalisation (no cellulitis cases required inpatient admission), and (c) likely prevented costly cellulitis complications in at least a subset of these patients.

Many patients with high bacterial loads fail to mount the classic signs and symptoms of infection[16,18] (CSS), thus reliance on clinical signs and symptoms alone to identify the presence of bacteria results in many wounds with bacterial burden missed by clinical examination and reactive wound care strategies. Here we observe that even in patients where invasive extension of bacteria from wounds contributed to cellulitis, CSS was highly variable. A reactive treatment approach in these patients after CSS mount may be particularly detrimental as cellulitis can progress quickly, producing more severe complications that require costly treatment, including hospitalisation.[12] Fluorescence imaging of bacteria has emerged as a solution for earlier detection of elevated bacterial burden in wounds. Clinical trials have repeatedly demonstrated that the presence of red or cyan on fluorescence scans is highly predictive of high levels of bacteria.[16-18,23,28] With a positive predictive value of 93% to 100% of red and cyan fluorescence signals across these studies, microbiology is not required solely to validate imaging findings, and treatment decisions based on the fluorescence scan information can be made immediately.[16-18,23,26,28] The observation of fluorescence from bacteria observed in and around the wound bed and periwound has been reported previously.[25,29-31] In this study, and distinct to wound-related cellulitis, a pattern of fluorescence from bacteria was observed to extend beyond the periwound region and could not be completely eradicated through cleansing and debridement alone. These imaging findings enabled differentiation between a colonised or inflamed wounds (ie, resulting from stasis dermatitis) compared with a colonised wound with wound-related cellulitis. In many of these cases, the presence of red fluorescence alerted the clinician to regions of elevated bacterial burden ahead of overt infection mounting as there were no obvious signs of infection in the tissue regions surrounding the periwound and wound bed. Given that at least 30% of cellulitis cases are misdiagnosed,[10,12] the addition of consistent and objective information provided by fluorescence scans can significantly reduce the uncertainty associated with cellulitis diagnosis. Additionally, in the 221 wounds not diagnosed with wound-related cellulitis, the use of fluorescence scans to aid in detection and source control of the bacterial burden may have prevented the progression of infection in some patients.

To limit the progression of cellulitis, proper wound bed treatment is also essential and includes thorough debridement with removal of necrotic tissue and bacteria demonstrated by fluorescent scanning. Debridement guided by fluorescent imaging results in the eradication of bacteria in addition to factors that can facilitate bacterial accumulation or impede healing (ie, necrotic tissue, slough, infected hematoma, or abscess).[32-34] The use of fluorescence scans in the outpatient setting enabled real-time evaluation of the efficacy of traditional strategies such as cleaning and debridement that are used to prepare the wound bed and control the source of bacterial infection. This is consistent with prior reports in which (a) fluorescence information aided wound bed preparation in >85% of wounds,[16,23] (b) wound bed preparation aided by fluorescence information was associated with an increase in 12-week healing rate and 33% decrease in antibiotic prescribing,[30] and is in line with recently published consensus guidelines.[26] In the current study, there were several instances where persistence of red fluorescence signals after these traditional strategies were used indicated that they were insufficient. Together with the irregular pattern of fluorescence extending outside the wound region that suggested cellulitis, this supported the decision to immediately initiate oral antibiotics. This swift initiation of oral antibiotics in patients with wound-related cellulitis was effective in rapidly reducing bacterial burden and limiting cellulitis from progressing, evidenced by none of the patients requiring hospitalisation or I.V. (intravenous) antibiotics and by the reduced bacterial signals on scans at subsequent visits to closely monitor progression. In contrast, the typical course of treatment for cellulitis often includes I.V. antibiotics and a median length of hospital stay of 5 days,[35] and is estimated to amount to a median cost of $2087 USD per day.[36] The use of fluorescence imaging to detect and manage wound-related cellulitis can mitigate the progression of infection and, in turn, avoid further antibiotic courses and the high costs associated with inpatient admission.

4.1 | Limitations

This investigation was performed at a single institution and, although there was a large patient volume and range of demographics included, additional studies are needed to assess the generalizability of our findings. Because of the observational nature of the study, we are unable to infer how lack of fluorescence imaging information may have impacted patient outcomes. Additionally, fluorescence imaging has a maximum detection depth of 1.5 mm[24] and does not provide information on non-bacterial components (eg, fungi) that may be present.[21] Another limitation was

the lack of comparison to "gold standard" diagnosis; this was not possible as there is no gold standard for diagnosing this invasive extension of bacteria. Although microbiology could confirm bacterial species and load, it is unable to indicate its spatial distribution or degree of tissue invasion. Furthermore, clinical signs and symptoms may not mount until well after the invasion of bacteria into surrounding tissue, forcing reactive care. In the future, fluorescence scanning for bacterial location may become a key component of gold standard wound-related cellulitis diagnosis.

5 | CONCLUSION

Cellulitis associated with chronic wounds presents a diagnostic dilemma, especially in the face of stasis dermatitis or inflammatory changes surrounding a wound. If early cellulitis is unrecognised and untreated, the cellulitis may progress, resulting in more tissue loss, progressive cellulitis requiring hospitalisation and I.V. antibiotics, and spread to other tissues including osteomyelitis or endocarditis. Invasive extension of bacteria into surrounding tissue may be missed utilising clinical criteria alone. The use of point-of-care fluorescence imaging provides objective information that enhances detection of wounds with elevated bacterial burden and more effective treatment. Here we show that early diagnosis and treatment with thorough source control using traditional and antimicrobial strategies guided by fluorescence imaging resulted in resolution of invasive extension of bacteria, no further progression of cellulitis, and wound healing.

CONFLICT OF INTEREST

Dr Charles A. Andersen has received funding from MolecuLight for speaking engagements. No funding was received to perform this study.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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