Can Fluorescence Imaging Predict the Success of CTPs for Wound Closure and Save Costs?

This author presents information on a pilot case series comparing clinical visual judgment to bacterial fluorescence imaging, revealing the power of visualization to predict cost savings for cellular- and tissue-based products (CTPs) and provide decision support.

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Clinicians do not have standard methods to determine the most appropriate time to apply skin grafts in a chronic wound or cellular- and tissue-based products (CTPs). If applied weekly over the course of 4 weeks, the cost of using CTPs is estimated to be over $6,400, with an additional $1,260 in facility fees and clinician time to manage chronic wounds in an outpatient facility. Being able to predict wound readiness accurately would greatly contribute to cost savings.

This case series compares clinical examination versus real-time bacterial fluorescence imaging (MolecuLight™ i:X, MolecuLight, Toronto Canada) to predict the effectiveness of the CTP and/or skin graft procedure in two patients undergoing weekly wound care and then receiving a CTP. The clinician relied on clinical examination to guide decisions to apply the CTP, as the clinician was blinded to fluorescence imaging results.

In each case, clinical examination indicated readiness for CTPs, yet fluorescence imaging revealed a significant bacterial burden (>10^4 CFU/g) prior to and following application of cellular tissue products. In both cases, the wounds failed to heal or make significant progress within a 30-day period. These results suggest that the MolecuLight i:X fluorescence imaging device provides objective information on wound bed readiness that can be used to support evidence-based decision making regarding wound care and treatment options, thereby creating the potential to save more than $7,660 in costs associated with failed CTP application over a 4-week period. Going forward, fluorescence imaging may serve as a real-time biomarker of high bacteria loads, facilitating more accurate debridement and optimizing wound bed preparation. Better bacterial management may lead to more rapid readiness for use of CTPs.

WHAT YOU SHOULD KNOW ABOUT BACTERIAL BURDEN AND BIOMARKERS

The presence of bacteria is a contraindication to the use of CTPs, as bacterial colonization in chronic wounds can hinder these products' effectiveness.[1] In one study, failure to reduce bacterial presence prior to grafting resulted in <20% graft take or complete graft loss.[2] In another study, which had 82 patients with venous leg ulcers, the presence of *Pseudomonas aeruginosa* was the only significant predictor of partial take or rejection of split thickness skin grafts (STSG).[3] Thus, if there is contamination, the application of CTPs should be delayed until contamination is addressed. Currently, there are no standard methods to objectively determine the most appropriate time to apply CTPs or proceed with skin grafting in a chronic wound. It is not the standard of care to perform tissue cultures or biopsies to determine wound bed contamination or infection prior to the use of CTPs or skin grafts.

Bacterial burden is typically assessed through clinical evaluation of the classic signs of wound infection. Clinical judgment and the manufacturer's instructions are used to determine the wound bed readiness for cellular tissue products and for continued assessment of wound closure. However, many of the classic signs and symptoms clinicians rely on to decide on treatment are often absent or go unrecognized in chronic wounds.[4,5] This makes accurate assessment of wound readiness challenging and may also contribute to the mounting costs

associated with graft failure and management of chronic wounds.

Previous studies have alluded to the use of biomarkers to objectively assess wounds to aid in the timing of applying cellular tissue products and guide therapy.[6] The use of biomarkers could result in earlier wound closure and reduce healthcare costs. However, the feasibility of utilizing biomarkers is limited by the time and access to facilities required for sample analysis. Alternative solutions that guide treatment by providing objective information in real-time are required.

REAL-TIME VISUALIZATION OF BACTERIAL FLUORESCENCE TO SUPPORT WOUND ASSESSMENT

The MolecuLight i:X imaging device can be used at point-of-care to assist clinicians in the assessment of wound readiness for CTPs by visualizing bacterial fluorescence in real-time, at the patient's bedside (**Figure 1**). The MolecuLight i:X provides instant, non-invasive visual detection and documentation of moderate to heavy bacterial loads (≥10^4 CFU/g) in wounds, which would otherwise be invisible to the naked eye.[7] Visualization of the distribution of moderate-to-heavy bacterial loads in and around the wound provides an objective biomarker to support treatment decisions. The MolecuLight i:X emits a narrow band of safe 405-nm violet-colored excitation light that illuminates the wound tissue and surrounding area, resulting in endogenous production of fluorescence signals, without need for additional contrast agents.[8]

The spectrum of signals (colors) produced depends on the composition of the biological and non-biological sources being excited and imaged. Violet light excitation of tissue components (e.g., collagen) produces green fluorescence.[8] Most bacteria fluoresce red as a result of porphyrin, a byproduct of bacterial heme production that is an endogenous fluorophore.[9] *P aeruginosa* uniquely produces endogenous pyoverdines, which creates a distinct cyan fluorescence when excited.[10] Optical filters in the MolecuLight i:X device allow fluorescence signals from wavelengths associated with bacterial fluorescence (red and cyan) and a narrow range of tissue fluorescence (green) to pass through the sensor and form the real-time image.[8] The filter also prevents reflected violet light from contaminating the image without any digital processing.

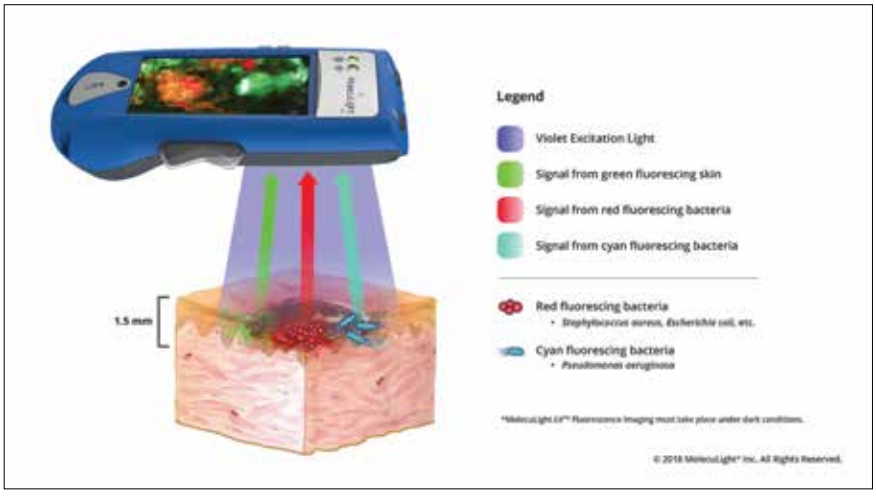

FIGURE 1. The MolecuLight i:X™ illuminated with safe violet (405 nm) light and filters out non-informative fluorescence signals with a dual bandpass optical filter. Image capture software allows for documentation (through photo and/or video capture) of the fluorescent signals that were observed in real-time. Red and cyan fluorescence on the images is indicative of moderate-to-heavy bacterial loads.

The use of fluorescence imaging, in combination with clinical judgment, can be an informative and reliable decision support for clinicians seeking to determine the appropriate time to apply cellular tissue products and for the ongoing assessment of wound progression. The MolecuLight i:X device can detect bacteria at and below the wound surface (typically to 1.5 mm deep). When debriding a wound, fluorescence imaging may reveal bacteria in deeper parts of the wound that may not be visible to the naked eye, enabling a more thorough debridement. In addition to tracking bacterial fluorescence, the MolecuLight i:X also captures standard wound images and measures wound area. The capacity to accurately measure wound area helps to ensure correct billing of procedures.

COMPARING CLINICAL VISUAL JUDGMENT TO BACTERIAL FLUORESCENCE IMAGES USING THE MOLECULIGHT I:X IMAGING DEVICE

To evaluate whether fluorescence imaging is an effective biomarker to support treatment decisions for patients receiving cellular-based products for wound closure, a prospective, single-site, double-blind case series was conducted. The IntegReview IRB-approved case series compared the effectiveness of clinical examination of chronic wounds alone to fluorescence imaging; the Moleculight i:X device was used to assess bioburden before and after application of cellular-based products. The goal of the study was to correlate predictions made with clinical examination or fluorescence imaging with predictors of success including 1) time to heal, 2) number of applications of tissue products, and 3) wound area reduction at four weeks. Patients with a chronic wound who were eligible to receive a CTP were able to participate in the study.

At the initial visit, clinical judgment based on visual inspection was used to determine if the wound was closed, healed, or completely epithelialized (all three terms were interchangeable). Afterward, a fluorescence image was taken (by a study nurse, to maintain study blinding) prior to the application of the skin substitute or skin graft by the clinician. The clinician was blinded to the fluorescence image until the conclusion of the study. Thereafter, fluorescence images of the wound were taken weekly over a five-week period.

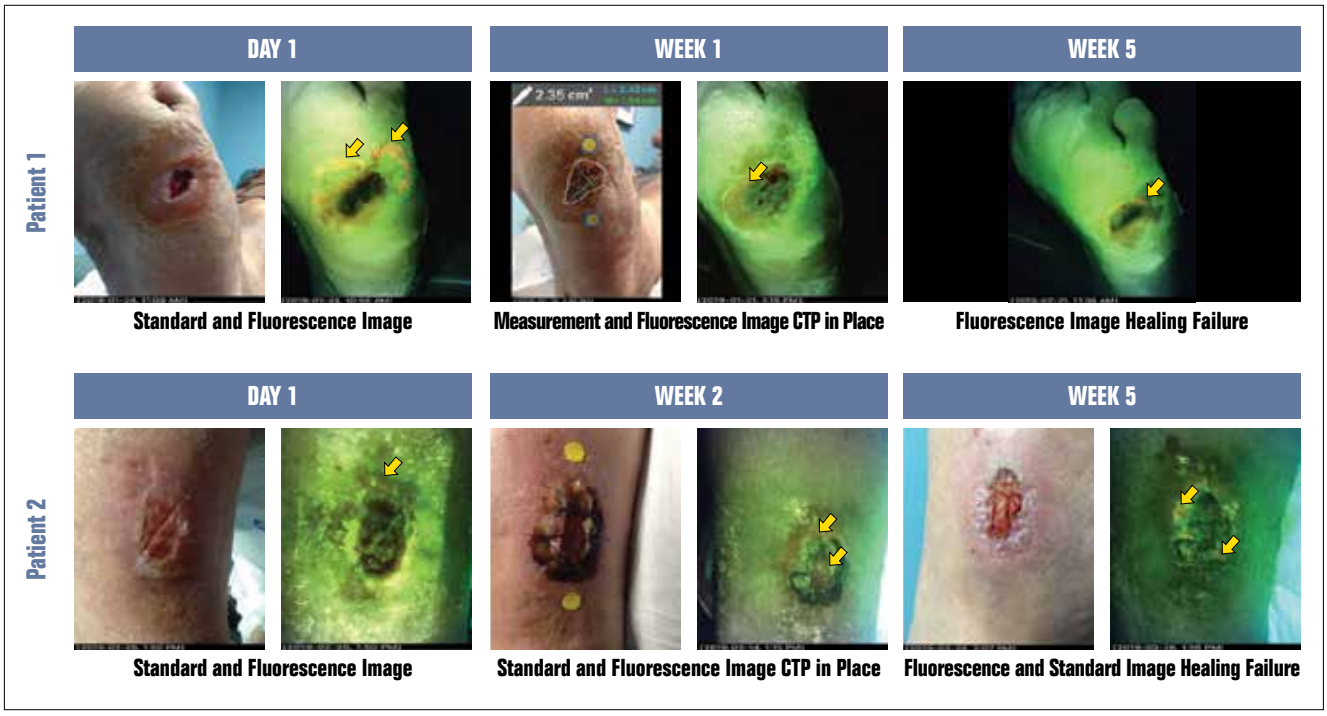

FIGURE 2. Two patients were imaged and evaluated for the presence of bacterial fluorescence, which would appear red/pink (pink or "blush red" has been linked to subsurface bacteria) or cyan (if Pseudomonas is present). On day 1, fluorescence images showed evidence of significant levels of bacteria in the peri-wound (arrows denote sites of red/pink fluorescence) without colonization in the wound bed. In week 2, wound bed bacterial fluorescence was also observed in the second patient. In both patients, bacterial fluorescence persisted to week 5, and the skin substitute applications failed to make progress, despite being deemed ready for tissue substitute application by the clinician.

The five patients were included in this pilot case series; thus far, two patients have completed the study and are the focus of this report. The displayed bacterial fluorescence on day 1 (data from after unblinding), even though the clinician's assessment indicated that the wound was ready for tissue substitute application based on standard of care. Fluorescence images taken prior to skin substitute application showed bacterial colonization at the peri-wound site without colonization in the wound bed (**Figure 2**).

In one patient, bacterial fluorescence was detected in the periphery of the wound on day 1. After five weeks, the wound failed to heal, and red fluorescence continued to be detected in the periphery of the wound. Similarly, the second patient exhibited red fluorescence at the wound periphery on day 1, and red fluorescence continued to be visible up to week five, at which point the wound had failed to heal. In both cases, the presence of bacterial fluorescence correlated with skin substitute failure. In hopes of publishing these findings, enrollment into the study is ongoing.

These study findings suggest that fluorescence imaging proved superior to clinician assessment alone when determining whether bacteria are present at loads contraindicated for grafting in wounds. Bacterial fluorescence information provided by the MolecuLight i:X imaging device serves as a diagnostic biomarker that facilitates evidence-based practice and guides appropriate corrections to timing and treatment of wounds prior to application of skin substitutes. The judicious, objective assessment of wound beds prior to use of skin grafts or cellular-based therapies can have significant implications for cost containment. It is well-established that clinical signs and symptoms alone have poor sensitivity in identifying the degree of contamination in a wound.[11] Having the ability to objectively assess bacterial load in a wound using fluorescence imaging can change wound care management by limiting the over-utilization of CTPs and providing real-time information to guide appropriate treatment.

WHY THIS TECHNOLOGY CAN POTENTIALLY CHANGE THE WAY WE DELIVER WOUND CARE

As of January 1, 2017, a new payment system for physicians was implemented. Physicians will no longer see Medicare Physician Fee Schedule increases/decreases at the end of each year; Medicare allowable rates will remain flat starting in 2019. The Quality Payment Program will provide either bonuses or deductions from the cur-

rent published fee schedule based on four performance categories:

- Quality
- Advancing Care Information
- Clinical Practice Improvement Activities
- Total cost of care (not just the cost of an item or a procedure)

The goal of the Quality Payment Program is to place greater focus on quality of care and total cost of care based on clinical practice guidelines with better use of electronic health records to communicate across the continuum of care. Physicians will need to develop wound care plans based on these four performance categories, focusing on value-based care rather than volume-based care in order to be prepared for the "bundled payments" that all payers are likely to adopt for wound care in the near future. As Fife notes, "Physician payment will be linked to quality measure performance, not really because of the Merit-based Incentive Payment System (MIPS) but because private payers will create differential reimbursement rates based on quality performance. Quality data are now publicly reported by practitioner name. Private payer use these scores to negotiate payment rates with physicians and to develop capitated payment rates."[12]

CTPs used to treat chronic wounds are expensive—the average cost is $1,600.

As the Centers for Medicare and Medicaid Services (CMS) move deeper into payment bundles for costs of wound care into a facility fee based on comorbidities (e.g., diabetes), poor wound progress and failed grafts/CTPs hinder patient outcomes and take away funding that can be allocated for other treatments; private payers will likely adopt this model as they determine cost savings using this type of reimbursement rather than the current fee-for-service (FFS) model.

Physician Compare is now a reality, where the public has access to the "quality of care" grade that you as a provider are given. There is also a published hospital grading to indicate the care that potential patients may receive at a given facility. This may lead to wound healing programs being linked to some sort of accreditation of the facilities (which is not the case at this time).

The importance of having or using objective measures is to: 1) determine wound bed readiness, 2) monitor thorough debridement of the wound on a weekly basis, 3) to ensure grafting will be successful, and 4) allocate resources more appropriately; and 5) report wound healing quality measures will become more important for a sustainable wound care business as we continue to move from our current FFS model to a pay-for-performance model.

FINAL THOUGHTS

In adopting any new modality, I am often asked a few questions by the audience at lectures: Is it covered? What is the code? How much does it cost?

Stay tuned, as these questions will soon be announced by the American Medical Association (AMA). Specific coding language will be available in January with the addition of new Category III codes to report "wound bacterial localization and treatment" with the effective date of July 1, 2020 to enable a reimbursement pathway for point-of-care fluorescence wound imaging. Reimbursement for procedures reported with a Category III code is at the payer's discretion.

As these procedures become more commonly adopted and established, MolecuLight will continue to work with the AMA to move these codes from Category III to Category I CPT status. Additionally, with the use of this novel device, larger studies are warranted to validate the results of the small pilot study being reported here. ■

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