Difficult-to-heal wounds of mixed arterial/venous and venous etiology: a cost-effectiveness analysis of extracellular matrix

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Importance: Difficult-to-heal wounds pose clinical and economic challenges, and cost-effective treatment options are needed.

Objective: The aim of this study is to determine the cost-effectiveness of extracellular matrix (ECM) relative to standard of care (SC) on wound closure for the treatment of mixed arterial/venous (A/V) or venous leg ulcers (VLUs).

Design, setting, and participants: A two-stage Markov model was used to predict the expected costs and outcomes of wound closure for ECM and SC. Outcome data used in the analysis were taken from an 8-week randomized clinical trial that directly compared ECM and SC. Patients were followed up for an additional 6 months to assess wound closure. Forty-eight patients completed the study; 25 for ECM and 23 for SC. SC was defined as a standard moist wound dressing. Transition probabilities for the Markov states were estimated from the clinical trial.

Main outcomes and measures: The economic outcome of interest was direct cost per closed-wound week. Resource utilization was based on the treatment regimen used in the clinical trial. Costs were derived from standard cost references. The payer’s perspective was taken.

Results: ECM-treated wounds closed, on average, after 5.4 weeks of treatment, compared with 8.3 weeks for SC wounds (P=0.02). Furthermore, complete wound closure was significantly higher in patients treated with ECM (P<0.05), with 20 wounds closed in the ECM group (80%) and 15 wounds closed in the SC group (65%). After 8 months, patients treated with ECM had substantially higher closed-wound weeks compared with SC (26.0 weeks versus 22.0 weeks, respectively). Expected direct costs per patient were $2,527 for ECM and $2,540 for SC (a cost savings of $13).

Conclusion and relevance: ECM yielded better clinical outcomes at a slightly lower cost in patients with mixed A/V and VLUs. ECM is an effective treatment for wound healing and should be considered for use in the management of mixed A/V and VLUs.

Keywords: extracellular matrix, adjunct therapy, venous leg ulcers, wound care, compression therapy, economic outcomes

Introduction
Difficult-to-heal chronic wounds often require care for several months. Even when good wound care practices are used, healing rates remain low. Venous leg ulcers (VLUs) require an average of 24 weeks to heal; however, approximately 15% of VLUs never heal, and recurrence is common (15%–71%).1,2 For mixed arterial/venous (A/V) ulcers, healing rates vary from 23% to 64% for ulcers associated with severe and moderate arterial disease, respectively.3 Low healing rates in VLUs and mixed A/V ulcers indicate that current standard of care (SC) is often inadequate. New strategies should be
considered as alternatives to standard care (compression therapy, debridement, and maintenance of a moist wound environment).\textsuperscript{4} Initial healing rate of VLUs and percentage change in ulcer area after treatment initiation predict ulcer healing.\textsuperscript{5} A VLU treatment algorithm suggests that >40% wound closure after 4 weeks of conventional therapy is an appropriate surrogate marker to identify patients likely to achieve complete wound closure with SC.\textsuperscript{6} It is unlikely that patients with <40% closure after 4 weeks of conventional therapy will have complete wound healing and could benefit from alternative or advanced interventions.\textsuperscript{7} Chronic wounds do not typically follow proper wound healing process (hemostasis, inflammation, proliferation, and remodeling phases)\textsuperscript{8} and often become stalled in the inflammation or proliferation states.\textsuperscript{9} Chronic wounds cannot re-epithelialize owing to failure of keratinocyte migration rather than proliferation.\textsuperscript{10} Failure of migration may occur from lack of a functional extracellular matrix (ECM), where there may be deficiencies in fibronectin and collagen molecules.\textsuperscript{11–14} High concentrations of ECM-degrading proteases, misregulated rates of matrix repair and degradation, increased numbers of senescent fibroblasts, or altered cytokine expression and redistribution may impede ECM function in chronic wounds.\textsuperscript{15–19} Lack of a functional ECM could inhibit normal wound repair process.

Alternative avenues have explored advanced therapies using cellular/tissue-derived products (CTPs), such as ECM.\textsuperscript{20} ECM wound matrix is derived from a thin, translucent tunica submucosa layer of porcine small intestine. Once harvested, all living cells are removed from the biomaterial and it is sterilized and lyophilized to allow long-term storage.\textsuperscript{21,22} The low porosity value of ECM indicates that it may be an effective barrier to wound bed dehydration.\textsuperscript{23–25} In vitro data indicate that ECM wound matrix provides an environment that allows proper fibroblast and keratinocyte cell attachment, proliferation, and migration.\textsuperscript{26,27} ECM is fixed to wounds and is typically reapplied every 3–7 days until closure.\textsuperscript{28,29} The efficacy of ECM in the management of VLUs, mixed A/V ulcers, and diabetic foot ulcers has been established.\textsuperscript{20,30–32} Data suggest that difficult-to-heal chronic wounds benefit from natural ECM wound matrix replacement therapy, as it promotes angiogenesis, cellular growth, and wound closure.

Difficult-to-heal wounds pose clinical and economic challenges.\textsuperscript{34} Estimated annual payer burden of VLUs approached $15 billion as of 2014.\textsuperscript{35} Relative to non-VLU patients, VLU patients incurred additional annual incremental costs of $6,391 through Medicare, while those with private insurance incurred additional costs of $7,030.\textsuperscript{35} VLUs account for the loss of >2 million workdays/year.\textsuperscript{36} The primary objective of this study was to assess the cost-effectiveness of single-layer ECM (OASIS Wound Matrix\textsuperscript{®}; Cook Biotech Inc., West Lafayette, IN, USA) as an adjunct therapy to SC compared with SC alone on wound closure for the treatment of VLUs and mixed A/V ulcers.

**Methods**

**Study participants, design, and interventions**

Data were derived from an 8-week randomized clinical trial of adults aged ≥18 years with VLU or mixed A/V ulcer (determined by clinical/instrumental assessment).\textsuperscript{37} Fifty patients with lower leg ulcers of mixed A/V (n=23) and venous (n=27) etiology visiting the outpatient leg ulcer clinic at the Wound Healing Research Unit, Department of Dermatology, University of Pisa, Italy, were prospectively selected for enrollment into a randomized trial that was approved by the institutional review board and local ethics committee of the Azienda Ospedaliera Universitaria Pisana.\textsuperscript{37} Patients were required to provide written informed consent before the clinical trial. Eligible patients had VLU or mixed A/V leg ulcer with an ankle brachial index of 0.6–0.8, ulcer duration of >6 months, ulcer size ≥2.5 cm\textsuperscript{2}, and 50% granulation tissue on the wound bed.\textsuperscript{37}

Patients who met the inclusion/exclusion criteria were randomized to treatment with ECM (n=25) or with standard moist wound dressing (petrolatum-impregnated gauze; n=25) after written informed consent was received. ECM material was cut to a size slightly larger than the wound, positioned directly on the wound, and moistened with saline; a secondary nonadherent dressing was applied. In the SC group, ulcers were treated with petrolatum-impregnated gauze applied with a secondary nonadherent dressing.

Wound closure and dressing were assessed at baseline and weekly for up to 8 weeks. Time to complete healing, percentage of granulation tissue (assessed by validated color defragmentation software),\textsuperscript{38} signs of infection, surrounding skin aspect, and comfort at dressing change were measured by clinical assessment and digital planimetry and assessed weekly. To ensure patients were blinded, they were instructed to change only the secondary dressing at home and were evaluated twice a week in the clinic, where the investigators performed all clinical and instrumental evaluations. Patients were followed monthly for 32 weeks to assess wound closure after the conclusion of the trial.

**Economic analysis**

Markov models are designed to aid health care decision makers in clinical situations for events (ie, health states)
and to measure the burden of illness of specific health states as they transition over time. The patients are considered to be in one of a finite number of discrete health states that incorporate all clinically important events into transition probabilities from one health state to another. A Markov model (TreeAge Pro Version 2014; TreeAge Software, Inc., Williamstown, MA, USA) was developed to compare the clinical outcomes and costs of ECM versus SC using the wound closure rates to estimate the number of closed-wound weeks and the expected VLU and mixed A/V ulcer cost per patient. Outputs from the Markov model were then used to derive a cost-effectiveness ratio for each treatment group, defined as the expected cost per closed-wound week. Using this approach, results were derived over 32 weeks to estimate the number of closed-wound weeks per treatment arm, in addition to the average cost to achieve closure (primary clinical outcome).

Resource utilization was based on the average time to dressing change reported in the trial. Costs were derived from standard cost references and medical supply wholesalers in the USA. The number of ECM applications was based on the treatment regimen used in the trial. A sensitivity analysis was performed on all costs associated with treatment to test the robustness of the model’s assumptions (ie, variables selected for model input) on the results.

Model inputs
Time horizon
A 32-week time horizon was selected to model the total costs across the entire episode of care for both treatment groups for the length of the trial (including follow-up assessments). Costs associated with outpatient treatment accrued until wound closure.

Two-state Markov model and transition probabilities
A two-state Markov model was a cycle length of 1 week and was chosen to follow the closed (epithelialized) and unhealed stages of VLU and mixed A/V ulcers (Figure 1). State 1, the unhealed state, represents healing VLUs and mixed A/V ulcers and, consequently, the total costs associated with treatment in the outpatient setting (ie, clinic visits, application of a skin substitute product, and facility and physician reimbursement). State 2, the closed phase, represents a closed VLU or mixed A/V ulcer and, consequently, incurs no additional costs. The transition probabilities from the unhealed to the closed phase were determined using wound closure rates from the randomized clinical trial. At the end of 8 weeks, approximately 80% of patients in the ECM group were considered closed compared with 65% in the SC group. These probabilities were extrapolated through the follow-up phase of 32 weeks, assuming cumulative probability rates over time using equations described by Briggs et al. This time-dependent Markov model provides a robust method to modeling a chronic disease state, since the assumption of constant transition probabilities is considered too restrictive for applications in health care. These weekly transition rates were used to populate the Markov model and to analyze clinical and economic outcomes. No adverse events were observed with either treatment; therefore, additional complications such as infection were not considered in the Markov analysis. Furthermore, due to the short duration of the trial, recurrence was not measured.

Clinical outcomes definition
The clinical outcome for the Markov model was defined as “closed-wound weeks” and represents the expected number of weeks that the wound was closed over the 32-week trial. Complete healing in VLU and mixed A/V ulcer was defined as growth of epithelium over a denuded surface without evidence of bleeding or drainage. These results are presented as closed-wound weeks to effectively demonstrate the differences in the wound healing trajectories between the two treatment groups. Closed-wound weeks represent the average expected time, in weeks, that VLU and mixed A/V ulcers remain closed in the two comparative cohorts given their respective transition probabilities from the unhealed state to the healed state. Closed-wound weeks are a mathematical complement to open-wound weeks and represent a positive measure of clinical outcomes.

Economics outcomes definition
The analysis was from the perspective of the third-party payer, and only direct medical costs of care were considered. Costs were reported in 2015 US dollars. Because of the
short duration of the model, costs were not discounted. A cost-effectiveness analysis was performed assessing cost per closed-wound week on a per-patient basis. Derivation of costs is displayed in Table 1. Given the 2014 changes to the Hospital Outpatient Prospective Payment System rates, ECM was considered a low-cost skin substitute. New Hospital Outpatient Prospective Payment System rates represent a bundled payment of facility reimbursement and product cost. Costs for low-cost skin substitutes, physician reimbursement for application of a skin substitute, facility reimbursement for an outpatient established clinic visit, and physician evaluation and management visits were used per the results of the trial. The ECM-treated group required fewer dressing changes, more than doubling the number of days between dressing changes compared with the SC-treated group (2.1 versus 5.2, respectively; *P < 0.05*). Therefore, unit costs for ECM-treated ulcers were calculated at 1 visit/wk and SC-treated ulcers at 3 visits/wk.

Sensitivity analyses
Sensitivity analysis consists of change in the value of an input parameter to assess the magnitude of its effect on the final results of the analysis (ie, change in total cost of care and change in rates of healing). One-way sensitivity analyses test the robustness of the model’s assumptions on the results (ie, variables selected for model input). Deterministic sensitivity analysis assists with justification for the choice of variables included in the model, in addition to providing an explanation for the source of ranges used. Variables with uncertainty (ie, costs and healing rates) or expectation of sensitivity were selected for these analyses. Sensitivity analyses were conducted on the probability of healing for ECM and SC, the costs for the bundled facility and product payment, and the physician reimbursement. Due to the uncertainty that surrounds VLUs of various sizes and shapes in addition to varying costs of reimbursement per geographic region in the USA, a ±50% variance around the base case estimated were utilized to incorporate the varying rates of healing and costs to assess the robustness of the model’s results.

Probabilistic sensitivity analysis was performed to evaluate parameter uncertainty by using a second-order Monte Carlo simulation of 10,000 trials; all model inputs were varied simultaneously. The cost-effectiveness ratio was recalculated from the dummy data set; the process was repeated multiple times (ie, 10,000). Beta and gamma distributions were applied for transition probabilities and assessing variance in total cost of care, respectively.

Results
Of the 50 patients who enrolled, 48 completed the study (two discontinued due to relocation). There were 25 and 23 patients in the ECM-treated and SC-treated groups, respectively. No significant differences were observed between the two groups with respect to demographics and ulcer and duration (Table 2). Average wound surface was 23.5 cm² for ECM and 25.2 cm² for SC. Before initiation of treatment, the average wound age was 7.2 weeks for the ECM group and 6.9 weeks for the SC group.

After 8 weeks, ECM-treated wounds healed in 5.4 weeks (mean) compared with 8.3 in the SC group (Figure 1). Complete wound closure occurred in 80% (n=20) and 65% (n=15) of the ECM-treated and SC-treated wounds, respectively. For wounds that did not close within 8 weeks, granulation tissue in the wound bed increased 30% (from 50% at baseline to 65% at 8 weeks) in the ECM-treated group and decreased 24% (from 50% at baseline to 38% at 8 weeks) in the SC-treated group (*P < 0.05*). No adverse events occurred with either treatment. Projected closure rates were greater for the ECM group compared with SC group (98% versus 91%, respectively).

Economic results
The primary clinical outcome for this economic analysis was closed-wound weeks. On the basis of the transition rate of the

Table 1

<table>
<thead>
<tr>
<th>Resource</th>
<th>Quantity</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOPPS rate low cost skin substitute (C5271)</td>
<td>1 visit/wk</td>
<td>$430.12</td>
</tr>
<tr>
<td>Physician rate skin substitute application (CPT 15271)</td>
<td>1 visit/wk</td>
<td>$87.24</td>
</tr>
<tr>
<td>OPPS rate hospital outpatient clinic visit (G0463)</td>
<td>3 visits/wk</td>
<td>$294.18</td>
</tr>
<tr>
<td>Physician rate evaluation and management visit level 2 (CPT 99212)</td>
<td>3 visits/wk</td>
<td>$77.34</td>
</tr>
</tbody>
</table>

Note: Healthcare Common Procedure Coding System (HCPCS) stated.

Abbreviations: CPT, Current Procedural Terminology; OPPS, Outpatient Prospective Payment System; wk, week.

Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>ECM (n=25)</th>
<th>SC (n=23)</th>
<th><em>P</em>-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>52</td>
<td>48</td>
<td>NSS</td>
</tr>
<tr>
<td>Ulcer size, mean, cm²</td>
<td>23.5</td>
<td>25.2</td>
<td>NSS</td>
</tr>
<tr>
<td>Ulcer duration, mean, wk</td>
<td>7.2</td>
<td>6.9</td>
<td>NSS</td>
</tr>
</tbody>
</table>

Note: Data were analyzed using Analysis of Variance (ANOVA) for multiple comparisons (SPSS 10 for Windows), with the significance level set at *P* < 0.05. Additionally, Male % significance was tested via a chi-square and Ulcer size and Ulcer duration were tested via a student’s *t*-test.

Abbreviations: ECM, extracellular matrix; NSS, not statistically significant; SC, standard of care; wk, week.
prospective clinical trial data, the expected number of closed-wound weeks accumulated over 32 weeks was higher for the ECM-treated arm (26.0 weeks for ECM versus 22.0 weeks for SC, respectively) (Figure 2). To provide another perspective, the clinical complement to closed-wound weeks is open-wound weeks. Consequently, the expected number of open-wound weeks for the ECM and SC cohorts was estimated at 6.0 weeks and 10.0 weeks, respectively. It is important to note that there is a 4-week difference (~1 month) in wound closure between ECM and SC. Patients receiving the SC treatment would have, on average, four additional open-wound weeks compared with patients treated with ECM wound matrix. These results indicate that ECM is more clinically effective than SC alone for the management of difficult-to-heal VLUs and mixed A/V ulcers.

Expected costs per ulcer at the end of the 32-week phase were $2,527 and $2,540 for the ECM and SC groups, respectively, which equates to a cost savings of $13 for the ECM-treated group. Therefore, ECM was economically dominant, providing better clinical outcomes at a slightly lower cost compared with SC. The incremental cost-effectiveness ratio (ICER) for ECM was $3.75, indicating that for each $3.75 paid for ECM therapy, patients gained 1 closed-wound week. While differences in these costs are not substantially different, it is important to note that the clinical benefit of ECM surpasses that of SC by providing, on average, an additional month of wound closure.

**Sensitivity analyses**

One-way deterministic sensitivity analysis revealed no thresholds where the primary findings changed. The most influential variables were the Outpatient Prospective Payment System reimbursement for a hospital outpatient clinic visit, the probability of healing on SC weeks 1–8, and the physician reimbursement for evaluation and management visits. All model inputs were considered in the sensitivity analysis. The values of these inputs were derived from CPT and Healthcare Common Procedure Coding System codes for 2015 Medicare-allowable total expected costs. When visits per week in the SC group were varied to two visits, ECM-treated ulcers still provided greater clinical outcomes but at a slightly higher cost ($2,527 for ECM and $1,885 for SC-treated ulcers).

Probabilistic sensitivity analysis indicated that adjunct ECM had the highest average effectiveness of 26±1.2 closed-wound weeks, whereas SC had the lowest at 22±1.4 closed-wound weeks. The cost-effectiveness acceptability curve (Figure 3) illustrates the probability that any one strategy is cost-effective as a function of willingness to pay. Given a maximum acceptable ceiling ratio of $2,000/closed-wound week, the probability that ECM is cost-effective compared with SC is 95%. If a patient’s willingness to pay is $0, the probability that ECM is cost-effective compared with SC is 53%.

**Discussion**

ECM as adjunct therapy to SC provided greater clinical benefit at a marginally lower cost than SC over 32 weeks. Patients treated with ECM would pay no additional cost per week to gain 1 additional closed-wound week compared with SC alone. Hospital outpatient department visits for facility

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**Figure 2** Comparison of closed-wound weeks between a cellular/tissue-derived product treatment in relation to SC for the management of venous leg ulcers.

**Abbreviations:** ECM, extracellular matrix; SC, standard of care.
and physician in addition to the probability of healing on SC for weeks 1–8 exerted the greatest influence on expected total costs for VLU. This Markov model provided a robust method to model a chronic disease state, since the assumption of constant transition probabilities is considered too restrictive for applications in health care. When the ECM adjunct therapy was compared with SC alone, ECM provided higher clinical benefit at a marginally lower cost. The SC treatment arm had 10 open-wound weeks (mean) relative to the ECM treatment arm (6 weeks). The longer a wound remains in the unhealed health state, the greater the risk of infection, risk of amputation, additional costs of care for clinic and product visits, and decreased quality of life. If an individual is willing to pay no additional cost per closed-wound week, the likelihood that ECM is cost-effective is ∼53% relative to SC. However, if an individual is willing to pay an additional $300 per additional closed-wound week, then the likelihood that ECM is cost-effective increases to 85%, respectively. Given the low success rates of closure using SC, ECM could be considered a cost-effective alternative to SC alone for the management of VLUs.

Modeling direct costs of wound care therapy in conjunction with healing trajectories can be challenging. Furthermore, there is a lack of rigorous investigations examining the economic burden of treatments for the management of VLUs. Carter et al found that ECM provided similar clinical outcomes at a substantially lower cost than other CTPs (−$3,900 less compared with human skin equivalent and −$4,500 less relative to living skin equivalent). Relative to SC, ECM costs an additional $600 annually, but provided seven additional closed-wound weeks. Similar results were found in a study by Hankin et al who evaluated the clinical and economic efficacy of ECM, human skin equivalent, and Talymed as an adjunct to SC compared with SC alone for the treatment of chronic VLUs and found ICERs per additionally successfully treated patient were $1,600 for Talymed, $3,150 for ECM, and $29,952 for human skin equivalent after 24 weeks. Results from this study for ECM at 32 weeks (∼$2,527) are consistent with findings from both studies. In diabetic foot ulcers, ECM yielded similar clinical outcomes to human skin equivalent but at a significantly lower cost ($2,522 versus $3,889 over 12 weeks, respectively; 2015 US dollars). Previous cost-effectiveness analyses have found similar results when assessing the relative costs and benefits of CTPs in the management of VLUs. Schonfeld et al evaluated the cost-benefit of human skin equivalent in comparison to Unna’s boot as the SC using a semi-Markov model over a 1-year time horizon and found that rates of healing in the human skin equivalent group were ∼48.1% compared with 25.2% in SC patients. Annual costs for human skin equivalent were slightly more expensive than the annual cost for Unna’s boot patients ($12,807 versus $10,482, respectively; 1996 US dollars), with a calculated ICER of $800 per additional month of healing. Similar results comparing human skin

Figure 3 Cost-effectiveness acceptability curve by treatment. Abbreviations: ECM, extracellular matrix; SC, standard of care.
equivalent to SC have been found in other studies in the UK and Canada with human skin equivalent providing a higher clinical benefit at a slightly higher cost.\textsuperscript{51,52}

Closure rates in ECM-treated VLUs reported in the clinical trial used for this economic analysis are higher than those previously reported. A randomized clinical trial with 120 patients with chronic leg ulcers reported 55\% of ECM-treated chronic ulcers closed after 12 weeks of treatment.\textsuperscript{20} Interim analysis of another clinical trial reported similar closure rates (71\% of ECM-treated VLUs closed at 12 weeks).\textsuperscript{35} The majority of wounds in both studies ranged from 1 month to 1 year.\textsuperscript{20,53} A greater percentage of closed patients in this study might reflect that wounds were treated earlier in the progression from a slow-to-heal wound to a difficult-to-heal wound, as the majority of VLUs and mixed A/V ulcers in this trial were 6–7 weeks old.

Management of VLUs and mixed A/V ulcers remains challenging. The overall burden of illness for VLU comprises 2\% of health care expenditures for Western European countries and almost $15 billion annually in the USA.\textsuperscript{35,54–57} Distinct differences exist across countries in resource utilization, regarding treatment algorithms for VLUs.\textsuperscript{37} The majority of expenditures for Medicare patients were comprised of outpatient/physician and emergency department visits, whereas costs for hospitalizations and outpatient/physician office visits were highest among those with private insurance.\textsuperscript{35} Hospitalization was the primary cost driver for VLUs in Germany, whereas drugs and office nurse visits were primary drivers in the USA. Despite differences in health care provider practice patterns and resource utilization, health care expenditures and rates of closure for VLUs are similar between countries.\textsuperscript{55} Comparing costs between the UK and Sweden, total costs of care for chronic wounds were generally higher in Sweden.\textsuperscript{56} Although CTPs are rarely used in Europe, similar costs and outcomes support the argument that conventional treatment practices may be supplemented by other options, such as CTPs, in an attempt to overcome the pathophysiological challenges of difficult-to-heal chronic wounds. In the Netherlands, two treatment modalities exist for VLUs: conservative treatment (eg, compression therapy, local treatment, and leg elevation) and surgical treatment (eg, superficial and perforating vein ablation and deep vein reconstruction).\textsuperscript{54} Due to restricted access to advanced therapies, health care providers in the Netherlands suggest that surgery plus compression therapy is an effective treatment modality for VLU, which could escalate costs.\textsuperscript{54}

Certain limitations should be considered when interpreting these results. Data were derived from a clinical trial conducted at one outpatient leg clinic with a small patient sample; results are not generalizable to other SC methods, health care settings, or wounds types. Although study investigators were trained in a uniform manner to ensure consistent treatment application and techniques, performance bias is still possible. While patients were blinded to the treatment administered, this study was not double blinded; therefore, observation bias is possible. Ulcer recurrence was not captured in this model because it was not assessed in the clinical trial. Finally, while this trial was conducted outside the USA, the model was based on US physician practice patterns. Centers for Medicare and Medicaid Services recommends that usual dressing change for gauze dressings impregnated with other than water, normal saline, hydrogel, or zinc paste be changed up to once per day,\textsuperscript{58} thereby resulting in multiple potential weekly clinic visits if patients are unable to change their own dressing.

**Conclusion**

Advanced therapeutic intervention is often required for difficult-to-heal wounds, which frequently have dysfunctional ECM. ECM adjunct therapy provided more closed-wound weeks at a slightly lower cost of care compared with SC in the management of VLUs and mixed A/V ulcers. Depending on an individual’s willingness to pay, ECM can be considered a cost-effective alternative to SC alone for the management of VLUs. Earlier treatment of VLUs and mixed A/V ulcers with CTPs, although initially more expensive, may be more efficacious and less costly in the long term by preventing recurrence, infection, or hospitalization. Wound care treatment algorithms and practice patterns should be reviewed and updated to reflect findings from current research.

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**Author contributions**

Doctors Romanelli, Gilligan, Waycaster, and Dini had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Gilligan and Waycaster.
Acquisition, analysis, and interpretation of data: Romanelli, Gilligan, Waycaster, and Dini. Drafting of the manuscript: Gilligan and Tollen. Critical revision of the manuscript for important intellectual content: Romanelli, Gilligan, Waycaster, and Dini. Statistical analysis: Gilligan. Obtained funding: Not applicable. Administrative, technical, or material support: Not applicable. Study supervision: Romanelli, Gilligan, Waycaster, and Dini. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

Doctors Romanelli and Dini report no conflicts of interest in this work. Doctors Gilligan and Waycaster are employees of Smith and Nephew Inc. The authors report no other conflicts of interest in this work.

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