Use of Ovine-based Collagen Extracellular Matrix and Gentian Violet/Methylene Blue Antibacterial Foam Dressings to Help Improve Clinical Outcomes in Lower Extremity Wounds: A Retrospective Cohort Study

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Abstract: Dressings that provide broad spectrum metalloprotease reduction along with inherent aspects of an extracellular matrix may contribute to improved wound healing outcomes and shorter treatment times. Objective. The author performed a retrospective case series analysis to determine the clinical outcomes of regular debridement with the use of ovine-based collagen extracellular matrix dressings and gentian violet/methylene blue polyurethane antibacterial foam dressings in treating 53 patients with 53 chronic lower extremity wounds (diabetic foot ulcers [DFUs], venous leg ulcers, and heel pressure ulcers). Materials and Methods. Patients were treated twice weekly in an outpatient clinic for the first 4 weeks and weekly thereafter until closure. Results. Average body mass index (BMI) for the study population was 28.3, and the average patient age was 75.9 years. Mean percent wound surface area reduction at 4, 8, and 12 weeks was 38.5%, 73.3%, and 91.3%, respectively. Average time to closure for all wounds was 10.6 weeks (range, 5–24 weeks). All wounds were 100% reepithelialized by week 20 except 1 DFU that reepithelialized at week 24. The average cost of care for a single wound episode (from presentation to closure) was $2749.49. Conclusion. Results of this analysis showed that the healing of chronic wounds in this series could be achieved at a reasonable cost with regular debridement and a collagen matrix dressing regimen, even in patients of advanced age and above average BMI as well as in wounds that did not achieve > 40% wound surface area reduction at 4 weeks.

Key words: antibacterial foam dressings, collagen extracellular matrix dressing, gentian violet/methylene blue, MMP reduction, ovine-based

Chronic lower extremity wounds are a significant cause of morbidity and a drain on health care resources worldwide as an increasingly prevalent and complex condition to treat. In the United States alone, chronic lower extremity ulcers affect an estimated 2.4 to 4.5 million people. Treatment costs for a venous leg ulcer (VLU) have been estimated at about $4000 per month and $16 000 per treatment episode, and recent research suggests an annual US payer burden of $14.9 billion. Diabetic foot ulcer (DFU) care adds between

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$9 billion to $13 billion to direct annual US government and private insurer costs associated with diabetes itself. Following holistic fundamentals of good clinical wound care is essential in successful management of chronic wounds and includes addressing factors such as systemic diseases, medications, offloading, nutrition, and tissue perfusion/oxygenation. Patient comorbid conditions, such as diabetes, renal failure, peripheral vascular disease, and smoking, can greatly influence healing; these conditions must be addressed to correct causes of tissue damage. A basic understanding of the pathological condition of a chronic wound is important in addressing cost and patient needs as well.

In addition to underlying medical conditions, chronic wounds are characterized by a complex etiology that can include abnormal cell-extracellular matrix (ECM) interactions, imbalances of matrix metalloproteinases (MMPs), elevated bioburden levels and bacterial biofilm, and a prolonged inflammatory response — all of which can damage the wound ECM. While MMPs are essential in normal healing, elevated MMP levels have been linked to wound failure. Elevated protease activity in a wound can break down the vital matrix and interfere with or change cell signaling.

A collagen dressing with a preserved structural component can serve as a provisional ECM dermal template and guide cellular interaction necessary to prompt keratinocyte migration. Dressings that provide broad spectrum MMP reduction, along with the inherent aspects of an ECM, may contribute to improved wound healing outcomes and shorter treatment times. Preliminary reports of an ovine-based collagen extracellular matrix (CECM) dressing (Endoform Dermal Template; Hollister Wound Care, Inc, Libertyville, IL) demonstrated the benefits in chronic wound healing. Ovine-based collagen extracellular matrix dressings are comprised of collagens I, III, and IV; they have been shown to retain the complex collagen architecture of native tissue ECM as well as ECM-associated secondary molecules including laminin, fibronectin, and glycosaminoglycans. The dressing has been shown in vitro to have buffering capacity for collagenases MMP-1, MMP-8, and MMP-13; stromelysins MMP-3 and MMP-10; MMP-12 and MMP-14; gelatinases MMP-2 and MMP-9; and neutrophil elastase. This broad spectrum of MMP inhibition may help protect against other detrimental MMP activity in the chronic wound microenvironment.

The purpose of this study was to analyze the clinical outcomes with the use of CECM dressings and gentian violet/methylene blue (GV/MB) antibacterial polyurethane (PU) foam (Hydrofera Blue; Hollister Wound Care, Inc, Libertyville, IL) dressings in treating chronic lower extremity wounds. The primary endpoint analyzed was mean percent wound surface area reduction at 4 weeks, and the secondary endpoint of the analysis was time to wound closure. Average treatment costs were also included in the analysis.

### Materials and Methods

A retrospective case series analysis of observational, longitudinal data collected from a single center was performed by a single investigator. Midlands Independent Institutional Review Board (IRB) reviewed this study and exempted it from IRB review under the Basic Health and Human Services Policy for Protection of Human Research Subjects (45 CFR §46). Records of patients with chronic full-thickness lower extremity ulcers (DFUs, VLUs, and pressure ulcers) that received treatment with CECM and GV/MB antibacterial PU foam dressings in an outpatient setting at the West Boca Center for Wound Healing in Boca Raton, Florida, between January 1, 2014, and January 31, 2015, were included in the analysis. Chronic was defined as a non-progressing wound of at least 4 weeks in duration.

All patients were treated twice weekly in the clinic for the first 4 weeks, and all wounds were treated in the following similar manner. During the initial visit, all patients completed a peripheral arterial disease screening questionnaire, which qualified or disqualified the need for vascular testing. Patients who underwent non-invasive arterial vascular testing, which showed an abnormal ankle brachial index and subtherapeutic skin perfusion pressure (< 50 mm Hg), were referred to vascular specialists.

### Table 1. Patient demographics

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
<th>Avg</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>53</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>22</td>
<td>41.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>31</td>
<td>58.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>75.9</td>
<td>12.4</td>
<td></td>
<td></td>
<td>33–101</td>
</tr>
<tr>
<td>BMI</td>
<td>28.3</td>
<td>5.1</td>
<td></td>
<td></td>
<td>17.4–43.3</td>
</tr>
<tr>
<td>Wounds treated</td>
<td>53</td>
<td></td>
<td>5.8</td>
<td>7.4</td>
<td>1.2–47.5</td>
</tr>
</tbody>
</table>

Avg: average; SD: standard deviation; BMI: body mass index
cular surgery for evaluation and potential intervention. Following adequate patient preparation, wounds were cleansed with saline or dermal cleanser and sharp surgical debridement as needed. Digital planimetry was not available at the treatment location, so basic linear measurements were used to calculate the wound area. Dimensions were recorded for length and width of each wound measured at the widest and longest points. A CECM dressing was hydrated with sterile saline and placed on the wound. A GV/MB antibacterial PU foam dressing was applied over the CECM dressing, followed by a secondary gauze dressing, and rolled gauze and/or compression as needed. Diabetic foot ulcers were offloaded as appropriate.

At the mid-week appointment, wounds were again cleansed and examined, but not surgically debrided. A new CECM dressing was applied when there was no visible evidence of the previous CECM dressing in the wound bed. After the initial 4-week period, patients received 1 weekly treatment consisting of cleansing, surgical debridement (as needed), application of CECM and GV/MB antibacterial PU foam dressings, and compression if appropriate until the wound closed.

Cost formula. Average cost per week during the first 4 weeks was calculated as per the following formula:

\[
\text{Cost per week} = \text{average charge for first evaluation and management (E/M Level 3) visit ($74.75) + debridement (97597) charge ($91.00) + average cost of CECM dressing ($11.50) + average cost of GV/MB antibacterial PU foam dressing ($6.50) + average charge for second E/M Level 3 visit ($74.75) + average cost of CECM dressing ($11.50) + average cost of GV/MB antibacterial PU foam dressing ($6.50) = $276.50.}
\]

Average cost per week during the subsequent weeks until wound closure (weeks 5–24) was calculated per the following formula:

\[
\text{Weeks 5–24 = average charge for E/M Level 3 ($74.75) or surgical debridement (97597) ($91.00) + average cost of CECM dressing ($11.50) + average cost of GV/MB antibacterial PU foam dressing ($6.50) = $270.50.}
\]

Results

In this case series, 53 patients with 53 wounds were treated. Of those, 31 (58.5%) were women and 22 men. The types of wounds treated were DFUs (n = 22), VLUs (n = 28), and pressure ulcers (n = 3). Average body mass index (BMI) of the study population was 28.3; average patient age was 75.9 years. The average wound surface area at first CECM dressing application was 5.8 cm$^2$. Patient demographics are presented in Table 1.

At 12 weeks, 31 out of 53 (58.5%) wounds were fully reepithelialized, and an additional 12 out of 53 (22.6%) of the remaining wounds were at least 80% closed. Mean percent wound surface area reduction by wound type at week 12 is shown in Figure 1. All wounds were 100% reepithelialized by week 20 except 1 DFU that reepithelialized at week 24. Average time to closure for all wounds was 10.6 weeks (range, 5–24 weeks). Outcomes by
and severe obesity (Figure 3A). The ulcer had been present since 2D) until the wound closed at 15 weeks (Figure 2E).

Five minutes after applying a sodium hypochlorite cleanser application, the wound bed was surgically debrided. A CECM dressing was applied and covered with a GV/MB antibacterial PU foam dressing and a secondary gauze dressing. Dressings were changed twice weekly for the first 4 weeks and once weekly thereafter (Figure 2B, 2C). After 4 weeks, dressings were changed once weekly (Figure 3D) until ulcer closed at week 8 (Figure 3E).

**Case 1: ankle wound with exposed tendon.** A 66-year-old man with diabetes presented with a left ankle wound with exposed anterior tibialis tendon (Figure 2A), secondary to excessively high pressure underneath a gauze wrap that was used to help treat the patient’s heel pressure ulcer. Prior to presentation at the clinic, the patient was self-treating the wound when he changed the dressing and over-tightened the gauze wrap. Patient had history of type 2 diabetes mellitus and human immunodeficiency virus. His glycated hemoglobin (HbA1c) was 7.6% and BMI was 28.78.

Five minutes after applying a sodium hypochlorite cleanser application, the wound bed was surgically debrided. A CECM dressing was applied and covered with a GV/MB antibacterial PU foam dressing and a secondary gauze dressing. Dressings were changed twice weekly for the first 4 weeks and once weekly thereafter (Figure 2B, 2D) until the wound closed at 15 weeks (Figure 2E).

**Case 2: VLU in an obese patient with diabetes.** A 93-year-old woman presented with a left lower leg venous insufficiency ulcer secondary to type 2 diabetes mellitus and severe obesity (Figure 3A). The ulcer had been present for 6 weeks prior to initial visit, during which time it was treated with hydrogen peroxide cleanser with antibiotic ointment and dry gauze changed daily. Her HbA1c measured 6.5% and BMI was 38.01.

Her wound was surgically debrided, and a CECM dressing was applied with a GV/MB antibacterial PU foam dressing cover, a secondary gauze dressing, and compression. The wound was debrided weekly, and dressings were changed twice weekly for the first 4 weeks (Figure 3B, 3C). After 4 weeks, dressings were changed once weekly (Figure 3D) until ulcer closed at week 8 (Figure 3E).

**Discussion.** Overall, debridement and the use of CECM dressings with GV/MB antibacterial PU foam dressings in an advanced age population with above normal BMI was successful with an average time to closure of 10.6 weeks for the wounds treated in this series. It is interesting to note that 27 out of 28 (96.4%) wounds that did not achieve > 40% wound surface area reduction by week 4 progressed to complete closure by week 20, with no additional wound treatment besides debridement and the CECM and GV/MB antibacterial PU foam dressing regimen. Further analysis found that patients with < 40% wound area reduction by week 4 had smaller wounds at presentation (4.8 cm² vs. 7.0 cm²), were older (77.4 years vs. 74.2 years), had a higher BMI (29.5 vs. 26.9), and averaged slower time to closure (12.7 weeks vs. 8.2 weeks), compared with patients who achieved ≥ 40% wound area reduction by week 4. Of those 25 wounds that achieved ≥ 40% wound area reduction by week 4, 21 (84%) were closed at week 12, compared with only 10 out of 28 (35.7%) wounds with ≤ 40% wound area reduction by week 4.

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**Table 2. Patient outcomes**

<table>
<thead>
<tr>
<th>Wound type</th>
<th>n (%)</th>
<th>Avg area at wk 0 (cm²)</th>
<th>Avg time to closure (wk)</th>
<th>Avg % area closed at wk 4</th>
<th>Avg % area closed at wk 8</th>
<th>Avg % area closed at wk 12</th>
<th>≥40% closed at wk 4 (%)</th>
<th>≥40% closed at wk 8 (%)</th>
<th>80%-99% closed at wk 12 (%)</th>
<th>100% closed at wk 12 (%)</th>
<th>100% closed at wk 20 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All wounds</td>
<td>53 (100)</td>
<td>5.8</td>
<td>10.6</td>
<td>38.5%</td>
<td>73.3%</td>
<td>91.3%</td>
<td>25 (47.2)</td>
<td>49 (92.5)</td>
<td>14 (26.4)</td>
<td>31 (58.5)</td>
<td>52 (98.1)</td>
</tr>
<tr>
<td>DFU</td>
<td>22 (41.5)</td>
<td>6.4</td>
<td>10.6</td>
<td>38.1%</td>
<td>76.5%</td>
<td>90.6%</td>
<td>11 (50.0)</td>
<td>20 (90.9)</td>
<td>9 (40.9)</td>
<td>13 (59.1)</td>
<td>21 (95.5)</td>
</tr>
<tr>
<td>VLU</td>
<td>28 (52.8)</td>
<td>5.8</td>
<td>10.4</td>
<td>39.2%</td>
<td>70.9%</td>
<td>92.6%</td>
<td>13 (46.4)</td>
<td>26 (92.9)</td>
<td>4 (14.3)</td>
<td>17 (60.7)</td>
<td>28 (100)</td>
</tr>
<tr>
<td>PrU</td>
<td>3 (5.7)</td>
<td>2.3</td>
<td>12.0</td>
<td>35.1%</td>
<td>72.0%</td>
<td>84.3%</td>
<td>1 (33.3)</td>
<td>3 (100)</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
<td>3 (100)</td>
</tr>
</tbody>
</table>

Avg: average; DFU: diabetic foot ulcer; VLU: venous leg ulcer; PrU: pressure ulcer
Compared with VLUs, DFUs showed a slightly greater percent wound surface area reduction rate at week 8, but a lesser area reduction at week 12. This is consistent with the author’s observation that DFUs in this series took longer than VLUs to progress to full closure during the reepithelialization phase, but considerably more research is required to validate this observation. No conclusions could be made regarding pressure ulcer healing in this series due to low subject numbers. Additionally, all wounds in this series were open for at least 4 weeks prior to initial presentation at the treating clinic. Since the author did not have access to the patients’ wound healing progression data prior to initiating CECM dressings, the change in healing trajectory with use of CECM dressings is unknown.

During the first 4 weeks of treatment, patients were seen twice weekly to more aggressively address inflammation and healing of the chronic lower extremity wounds and to verify dressing integrity. The aim was to quickly reduce elevated protease activity, especially MMP-9 (gelatinase B) prominence in the wound, as high levels of active MMP-9 have been implicated as an important contributor to delayed healing.\textsuperscript{17,18} In addition to dressing placement, the first weekly visit of the initial 4 weeks of treatment was focused on debridement and exudate management, wound was stable and progressing toward closure (usually by week 5), CECM dressings remained visible in the wounds for longer periods of up to 7 days.\textsuperscript{20} Based on this experience, and for the purpose of consistency, the author switched the clinic visit frequency to once weekly after the initial 4 weeks. In the author’s experience, a new CECM dressing should be placed about the time there is no visible presence on the wound bed of the previously placed CECM dressing. In all 53 patients in this series, there was no visible presence of CECM dressings upon removal of the cover dressing at any of the dressing changes, so in all cases, a new CECM dressing was placed at each dressing change.

Fife and Carter\textsuperscript{21} reported a mean cost to closure per wound in the US Wound Registry (5240 patients with 7099 wounds) of $3927. Average wound surface area was 19.5 cm\textsuperscript{2}, average patient age was 61.7 years, and mean number of serious comorbid conditions (mostly diabetes and obesity) was 1.8.\textsuperscript{21} Outcomes extracted from the Registry can be ideal “real world” comparators since the registry contains data of patients with multiple comorbidities treated in a variety of outpatient care settings, which reflects real-life practice.\textsuperscript{21} Elements of cost in the Registry included the billed advanced practitioner fee for one visit,
the billed facility fee for that day’s visit, billed procedure costs for that day (e.g., bioengineered skin application, debridement, compression bandaging), and the estimated cost of all wound care dressings and therapies over the whole course of treatment.

In the present series, the average per patient cost of episode of care was approximately $2749; this is 30% less than the average per patient cost of wound care reported in the Registry.21 Cost calculations for this analysis did not include compression bandaging or gauze, but otherwise included similar elements as the Registry. Compared to Registry data, the average wound surface area at presentation in the current series was smaller and average patient age was higher; these variables were not controlled for in the present analysis. In addition, patient care in this series took place at a single, free-standing wound clinic office of a qualified health care professional. Even allowing for these differences, it appears the cost of care to treat wounds in the present series was well under the real-world average, despite the effects of advanced age and multiple serious comorbidities on the patient population. It is conceivable that the smaller wound sizes in the patient population presented study here therein could have contributed to a lesser overall cost compared with Fife and Carter21; however, without direct treatment-to-dressing comparative data, these numbers can only be anecdotally reviewed and compared. Larger controlled cost studies are needed to quantify actual cost savings.

The CECM dressings are prepared from propria submucosa of ovine forestomach tissue sourced from New Zealand using processes to delaminate and decellularize the tissue.15,16 It has been proposed that the effectiveness of a CECM dressing is predicated in its structure as an intact collagen matrix dressing.11,22 Mechanisms of action of an intact collagen dressing include binding growth factors, regulating cell activity, facilitating intercellular communication, serving as a scaffold to hold cells together, and providing structural support to help tissue repair in both acute and chronic wounds.8

Instructions for the use of a CECM dressing call for securing the dressing with an appropriate cover such as a border foam dressing or any standard foam dressing. The cover dressing can be any secondary dressing that manages exudate appropriately. Any foam dressing can be placed for absorption. The author chose to use a foam dressing with broad spectrum antibacterial properties to help address bacterial bioburden, but the foam cover dressing does not need antibacterial properties for the function of the CECM dressing. The purpose of the GV/MB foam dressing was to facilitate wicking of wound exudate into the foam dressing and protect the wound from the external environment. The 2 organic pigments (methylene blue and gentian violet) bonded to the foam to create a microenvironment meant to inhibit the growth of microorganisms.23 The antibacterial and absorptive characteristics of the foam may have contributed an incremental effect on wound healing (but was not measured); any added or symbiotic effect, whether

Figure 3. Case 2: Venous leg ulcer (VLU) progression of wound to closure. (A) Left VLU at presentation (5.4 cm x 5.7 cm x 0.3 cm); (B) post debridement 1 week following use of collagen extracellular matrix (CECM) dressings with a gentian violet/methylene blue (GV/MB) antibacterial polyurethane (PU) foam dressing; (C) wound was 77% reepithelialized after 4 weeks of CECM dressings with GV/MB antibacterial PU foam dressing; (D) at week 6, wound was 96% closed; and (E) ulcer was fully reepithelialized at week 8.
beneficial or detrimental, of the cover dressing in this series is unknown. The author has observed similar effects on wounds with use of other foam cover dressings in combination with CECM dressings. A comparative study of wound healing outcomes with CECM dressings and various secondary cover dressings would be useful to guide product selection.

To the best of the author’s knowledge, this is the largest retrospective cohort study to date that documents the incremental rate of closure over time of chronic wounds treated with CECM dressings and GV/MB antimicrobial PU dressings. A previously published retrospective case series analysis\textsuperscript{13} of 23 VLU’s treated with CECM dressings and regular debridement reported that all 23 ulcers (100%) healed during an average of 7.3 weeks (range, 2–15 weeks). Mean percent wound surface area reduction of all wounds was 97.9% at week 12, and 50% of wounds treated with CECM were closed by 7 to 8 weeks.\textsuperscript{13} In the present study, only 4 out of 28 (14.3%) VLU’s were 100% closed at week 8. This difference could be caused by a variety of factors including the advanced age of the patients included herein compared with the patient population in Bohn and Gas\textsuperscript{13} (75.9 vs. 55.3 years).

The present results are similar to those of Liden and May\textsuperscript{12} in their evaluation of CECM dressings for the treatment of recalcitrant wounds, which included venous, diabetic, and incisional wounds, in 19 patients with 24 wounds. At 12 weeks, 50% of wounds had closed, and the mean percent wound surface area reduction was 73.4%.\textsuperscript{12} However, an accurate comparison of the present results with existing wound studies is difficult because of differences in study designs and samples.

The CECM dressings in the present study were placed only after appropriate debridement. The type of gauze wrap applied over the GV/MB antibacterial PU foam dressings was determined based on the level of exudate in the wound. An important cost aspect of ovine-based CECM dressings is that they are classified for reimbursement as a collagen dressing versus an advanced wound care matrix dressing, and therefore can be applied from the initial visit rather than waiting the requisite 3 to 8 weeks of moist wound healing dressing application typically required by the Centers for Medicare and Medicaid Services and private payers prior to initiating an advanced wound care matrix dressing.\textsuperscript{23,25} The dressings have a 36-month shelf life and can be applied by patients, physicians, nurses, or any other caregiver in any care setting.

Results of this analysis showed the healing of chronic wounds in this series could be achieved with regular debridement and a relatively inexpensive collagen matrix and antibacterial dressing regimen (compared to the respective overall cost of care in Fife and Carter\textsuperscript{21}), even in patients of advanced age, with an above average BMI, and in wounds that did not achieve > 40% wound surface area reduction by week 4. The data are promising but have all the limitations of an uncontrolled, retrospective case series analysis including lack of a comparator, patient selection bias, differences in wound care techniques between clinicians, and potential flaws in recordkeeping. The relatively small patient sample size and single-center site bias are additional limitations. A larger, controlled study of wound closure outcomes with both individual and combination use of CECM dressings and GV/MB antimicrobial PU dressings is needed to understand the incremental effect of each of the dressings on healing.

### Conclusion

Healing of chronic wounds in this series was achieved with regular debridement and a relatively inexpensive collagen matrix and antibacterial dressing regimen, even in patients of advanced age, with an above average BMI, and in wounds that did not achieve > 40% wound surface area reduction by week 4. The average cost of care for a single wound episode in this series was $2749, which was under the real-world mean cost to closure per wound of $3927 reported by Fife and Carter based on US Wound Registry data.\textsuperscript{21} Although this is the largest case series to date evaluating chronic wound closure with CECM dressings and GV/MB antimicrobial PU dressings, larger, controlled research is needed to determine the comparative cost and clinical effectiveness of this dressing combination in treating chronic lower extremity wounds.

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### Table 3. Mean cost to closure per wound in US Wound Registry versus the current study

<table>
<thead>
<tr>
<th></th>
<th>Patients (N)</th>
<th>Wounds (N)</th>
<th>Average wound surface area (cm(^2)) at admission</th>
<th>Average patient age</th>
<th>Mean serious comorbidity conditions (n)</th>
<th>Mean cost to closure per wound</th>
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<tr>
<td>US Wound Registry\textsuperscript{21}</td>
<td>5240</td>
<td>7099</td>
<td>19.5</td>
<td>61.7</td>
<td>1.8</td>
<td>$3927</td>
</tr>
<tr>
<td>Current study</td>
<td>53</td>
<td>53</td>
<td>5.8</td>
<td>75.9</td>
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<td>$2749</td>
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References


