Review

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Comparative cost and clinical effectiveness of clostridial collagenase ointment for chronic dermal ulcers

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Chronic dermal ulcers affect approximately 2.4–4.5 million people in the USA and are associated with loss of function, decreased quality of life and significant economic burden. Debridement is a critical component of wound care involving removal of nonviable tissue from chronic wounds to stimulate the granulation and epithelialization process. Clostridial collagenase ointment has been used as a method of wound debridement for more than 50 years and is currently the only enzymatic debriding ointment with US FDA approval. This review discusses the results of recent real-world studies that build upon the evidence demonstrating the clinical effectiveness, cost–effectiveness and safety of clostridial collagenase ointment across wound types and care settings.

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Background

Chronic dermal ulcers affect approximately 2.4–4.5 million people in the USA [1]. Predominantly affecting older individuals, the prevalence of chronic wounds is increasing with the aging of the population. The growing burden of treating chronic wounds is further exacerbated by increasing healthcare costs and an increase in the incidence of diabetes and obesity [2]. Chronic dermal ulcers (venous leg ulcers [VLUs], diabetic foot ulcers [DFUs] and pressure ulcers [PUs]) can lead to loss of function and productivity, anxiety and decreased quality of life [3]. Direct costs associated with chronic wounds and their care are estimated at more than US$33 billion annually in the USA [4–6]. A recent economic evaluation of Medicare beneficiaries revealed that approximately 14.5% of this population (8.2 million patients) were diagnosed in 2014 with at least one type of wound or wound-related infection, associated with a conservatively estimated cost of care of nearly US$32 billion [7]. These figures underestimate total costs as they do not account for the indirect costs associated with chronic wounds (e.g., loss of productivity, quality of life and absenteeism).

Debridement is a critical component of wound care involving removal of necrotic tissue, foreign debris, bacterial growth and callus from chronic wounds to stimulate the wound granulation, epithelialization and proliferation processes [8]. Methods of debridement include surgery (sharp debridement), enzymatic, autolytic, chemical (antiseptics, polysaccharide beads and pastes), biosurgical (maggots) and mechanical (hydrodebridement) [8]. These methods may be used individually or in combination to optimize the debridement process. The choice of debridement method is based on patient characteristics, wound type, potential for infection and available medical expertise and resources [9]. Sharp debridement removes necrotic tissue from the wound bed via use of scalpels, curettes, etc., and is considered the standard of care in many cases [1]. However, not all patients are surgical candidates, and

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utilization may be limited further by patients' bleeding tendency and pain tolerance [10]. Autolytic debridement (AD), promoted by hydrogels or hydrocolloid dressings, relies on the body's own enzymatic mechanisms to remove necrotic tissue [1,11]. As such, it is time consuming and associated with risk of infection [10]. Enzymatic debridement entails topical application of enzymes (collagenase) to digest and dissolve devitalized tissue in the wound.

Pharmacology of clostridial collagenase ointment

Clostridial collagenase ointment (CCO) is currently the only enzymatic debriding ointment that has US FDA approval and has been used as a method of wound debridement for more than 50 years [12]. Bacterial collagenase isolated from *Clostridium histolyticum* is a selective enzymatic agent that causes hydrolytic cleavage of collagen molecules, which are a major component of nonviable tissue in the wound bed [13]. CCO effectively and selectively removes detritus without harming healthy tissue, thus contributing to the formulation of granulation tissue and subsequent epithelialization of dermal ulcers [14].

A large body of experimental data suggests that, in addition to its debriding activity, CCO may actively promote healing by potentiating cellular migratory, proliferative and angiogenic responses to injury [13]. Further, CCO may decrease the excessive and prolonged inflammation associated with nonhealing wounds by downregulating inflammatory cytokines [15]. *In vitro* and *in vivo* studies suggest that these effects are mediated by biologically active matrix fragments or peptides liberated via specific cleavages made by CCO during the debridement process [13,15]. Unlike endogenous human collagenases, CCO cleaves collagen at multiple sites, thus facilitating the production of multiple bioactive peptides [16]. Galperin *et al.* demonstrated that in differentiated THP-1 monocytes, clostridial collagenase-digested collagens suppressed lipopolysaccharide-induced release of TNF-α and lL-6 [15]. Furthermore, in 17 patients with DFUs treated with CCO versus hydrogel, the level of analytes associated with resolution of inflammation increased while those associated with inflammation (TNF-α and IL-6) decreased [15].

Pharmacoepidemiology of CCO use

National wound registry data aggregated from electronic health records (EHRs) of hospital-based outpatient wound center patients revealed that between 13 and 20% of more than 28,000 DFUs, VLUs and PUs analyzed were treated with CCO [17–19]. The authors found that healthcare providers are using CCO in more severe, difficult-to-heal wounds; mean wound surface area was significantly larger in DFUs treated with CCO compared with wounds not treated with CCO (7.6 vs 5.4 cm^2, respectively; $p < 0.0001$), and the majority of PU wounds treated with CCO were stages III and IV (60.1 and 29.6%, respectively). In addition, relative to the overall population among all wound types, patients treated with CCO had substantially longer days in service and their wounds were more likely to receive debridement of all methods.

Only a small number of systematic reviews of the medical literature on the safety and effectiveness of CCO have been published in recent years. A systematic review by Ramundo and Gray published in 2009 analyzed 12 retrospective and prospective studies of CCO for treatment of PUs, leg ulcers or burn wounds: 5 randomized controlled trials (RCTs) compared CCO versus placebo and 7 studies compared CCO with alternative active debridement methods (e.g., hydrogel, silver sulfadiazine and autolysis) [20]. The authors determined that CCO is a selective, effective method for debridement of PUs, leg ulcers and burn wounds that has been used safely in adult, geriatric and pediatric populations. A recently published (2017) systematic review and meta-analysis by Patry and Blanchette analyzed 22 RCTs evaluating enzymatic debridement with CCO in all types of wounds and ulcers across all care settings [21]. The authors qualitatively summarized outcomes of collagenase either for wound healing or wound debridement and supported its use for enzymatic debridement in PUs, DFUs and in conjunction with topical antibiotics for burns [21]. Meta-analysis (n = 10 studies) was performed for the risk of adverse events (primary outcomes were not meta-analyzed). An increased risk of adverse events was calculated in patients treated with collagenase compared with alternative therapies (relative risk: 1.79; 95% CI: 1.24–2.59; $I^2 = 0\%$; $p = 0.002$). It should be noted that several studies were excluded from this analysis as two references were based on a single RCT, another RCT compared adverse events between different posology of collagenase and several studies did not report adverse events. Adverse events related to collagenase were seen in 11 of 17 RCTs (10 had values and relationships to adverse events made by authors). Subgroup analysis for significant adverse events related to collagenase or the alternative treatment (cellulitis was the only one suspected upon initial analysis) yielded no statistically significant relationships [21]. An examination of the individual studies included in this adverse event analysis reported infrequent pruritus, rash, edema, erythema (one case in one study), burning sensation at wound site (similar frequency between groups in several studies), burn bed infection (in a single study, seven cases with

collagenase vs one case in control group), herpes infection (one case in one study), mild bleeding (one case in one study) and cellulitis (several cases in several studies). However, the risk ratio of developing cellulitis was not found to be statistically significantly different between treatment groups on subgroup analysis by Patry *et al.* [21–30], and a high risk of bias was noted by the Cochrane risk of bias tool among the majority of RCTs included. The systematic review and meta-analysis contained information from some, but not all, of the more recent studies in the literature as it was limited to RCTs, excluding cohort (prospective or retrospective) studies.

Therefore, we performed a narrative review to discuss the results of more recent real-world studies that expand upon the RCT evidence base, to demonstrate the effectiveness and safety of CCO across wound types (VLU, PU, DFU, burns) and care settings (acute care, postacute care and long-term care) and illustrate the cost–effectiveness of CCO as a debridement option.

Discussion of clinical effectiveness

Several effectiveness studies and cost–effectiveness models reviewed here utilize real-world data from the US Wound Registry (USWR). These studies may be more generalizable to actual practice in hospital outpatient clinics compared with analyses based on RCTs, as the registry includes typical patients often excluded from RCTs [31,32]. As such, the USWR, which harnesses electronic healthcare data at point of care, offers ideal opportunities for comparative effectiveness research in wound care [31–33].

Effectiveness of CCO in debridement of PU

CCO has been studied for the treatment of PUs in several studies, both in the long-term care setting and in the outpatient setting, either as monotherapy versus AD with hydrogel or medicinal honey, or in combination with sharp debridement versus sharp debridement alone (Table 1) [12,34–37].

Milne *et al.* conducted a two-phase RCT on 27 patients with PUs residing in a long-term care facility, comparing CCO with AD plus hydrogel [34,35]. In the first phase of the study, which evaluated wound debridement for 6 weeks after randomization (based on Pressure Ulcer Scale for Healing Tool score and Wound Bed Score), CCO was superior to hydrogel in fully debriding nonviable tissue in 11 of 13 (85%) PUs versus 4 of 14 (29%) PUs in patients randomized to each treatment, respectively ($p < 0.003$). Of note, the mean wound size at baseline was significantly larger in the group treated with CCO (12.29 vs 7.90 cm^2, respectively) [35].

The second phase of the study recruited only patients with wounds that were completely debrided in each group 6 weeks after randomization; these patients were followed until wound closure or to day 84 [34]. Patients continued to receive either CCO or hydrogel on a daily basis, even though no visible devitalized tissue was present in the wounds. All patients (n = 3) in the hydrogel group reached complete epithelialization with a mean of 32.6 days, and 9 of 10 patients in the CCO group reached complete epithelialization with a mean of 45 days ($p = 0.121$; one patient in each group was eliminated within the first week). In aggregating Phase I and Phase II data, the closure rates at the end of the study were superior for collagenase (69%) versus hydrogel (21%; $p = 0.0213$). The authors concluded that these findings add to the evidence base that facilitating maintenance debridement, either by collagenase or hydrogel, can be used to complete wound closure when utilized in conjunction with a validated predictive wound healing tool that closely monitors therapy.

In a more recent publication, Waycaster *et al.* [36] report additional details and outcomes assessed in Phase I of the above study that further support the potential of CCO to improve clinical outcomes in patients with PUs in a long-term care setting. Patients treated in Phase I with CCO had a granulation rate approximately twice that of those receiving hydrogel (average 2% gain in granulation tissue per day vs 1% per day, respectively), and showed a significantly greater percentage of granulation tissue formation at week 6 ($p = 0.003$). Similarly, Wound Bed Score values improved more rapidly among patients treated with CCO, and improvements from baseline to week 6 were greater in patients who received CCO than in those treated with hydrogel (+4.6 vs +2.6 units, respectively). Patients treated with CCO also showed significant reductions in wound surface area from baseline (10.3 cm^2) to week 6 (2.1 cm^2; $p = 0.009$), which were not observed in hydrogel-treated patients.

The effectiveness of CCO has also been demonstrated in the hospital outpatient department setting, utilizing real-world data from the USWR [12,37]. Using an EHR purpose-built for wound care documentation, data transmitted to the USWR between 2007 and 2013 yielded 202 patients (337 stage IV PU wounds) treated with CCO plus selective sharp debridement (CCO group) and 232 patients (336 stage IV PU wounds) treated with selective sharp debridement alone (non-CCO group) [12]. The proportion of wounds closed at any time was two times greater in the CCO group compared with the non-CCO group (22.2% [75/337] vs 11.0% [37/336] at 1 year; $p < 0.0001$

Table 1. Recent clostridial collagenase ointment trials for debridement of pressure ulcers.

Study (year)	Patient population	Study design	Setting	Adjunct to SD	Comparator	End points	Results	Ref.
Gilligan *et al.* (2017)	PU (stages II, III and IV)	Retrospective review based on USWR	Hospital outpatient	Not necessarily; SD was permitted but not required by protocol	AD with honey	100% granulation and epithelialization at 1 year	CCO users had significantly fewer total visits (9.1 vs 12.6; $p < 0.001$), fewer total selective sharp debridement sessions (2.7 vs 4.4; $p < 0.001$) and fewer PUs receiving NPWT (29 vs 38%; $p = 0.002$) versus treatment with honey; CCO-treated PUs achieved faster rates of 100% granulation (255 vs 282 days; $p < 0.001$) and subsequent epithelialization (288 vs 308 days; $p = 0.011$) versus PUs treated with medicinal honey CCO-treated PUs were 38% more likely to achieve 100% granulation versus honey-treated PUs at 1 year ($p = 0.018$) CCO-treated PUs were 47% ($p = 0.024$) more likely to epithelialize at 1 year compared with PUs treated with honey	[37]
Milne *et al.* (2010)	PU (stages III and IV)	Prospective, randomized, single-blind trial	Long-term care facility	No	Hydrogel	Complete necrotic tissue debridement at day 42 based on weekly photographs evaluated with digital planimetry software, changes in PUSH Tool score and WBS	Ability of CCO to debride nonviable tissue fully within 42 days was superior to hydrogel: 11/13 (85%) versus 4/14 (29%) patients randomized to each modality, respectively, achieved complete debridement Reduction of nonviable tissue was greater on a weekly basis with CCO versus hydrogel ($p < 0.009$) Overall wound size decreased faster with CCO versus hydrogel ($p < 0.009$)	[35]
Waycaster *et al.* (2014)	PU (stages III and IV)	Prospective randomized single-blind trial	Long-term care facility	No	Hydrogel	Changes in WBS, tissue granulation, wound surface area and epithelialization	CCO: 2% gain in granulation tissue/day Hydrogel: 1% gain in granulation tissue/day WBS improvements from baseline to week 6 CCO: +4.6 units; hydrogel: +2.6 units Change in wound size from baseline to week 6 CCO: 10.3–2.1 cm^2; $p = 0.009$ Hydrogel: 6.5–3.0 cm^2; NS	[36]
McCallon and Frilot (2015)	PU	Retrospective cohort study	Long-term acute care hospital	No; adjunct to NPWT	NPWT alone	BWAT	Statistically significantly ($p < 0.05$) greater speed of wound healing (reduction of BWAT score: -2.34) and reduction of necrotic tissue (reduction of BWAT items 5 and 6: -2.39) with CCO + NPWT versus NPWT alone	[38]

AD: Autolytic debridement; BWAT: Bates–Jensen Wound Assessment Tool; CCO: Clostridial collagenase ointment; NPWT: Negative-pressure wound therapy; NS: Not significant; PU: Pressure ulcer; PUSH: Pressure Ulcer Scale for Healing; SD: Selective debridement; USWR: United States Wound Registry; WBS: Wound bed score.

Table 1. Recent clostridial collagenase ointment trials for debridement of pressure ulcers (cont.).

Study (year)	Patient population	Study design	Setting	Adjunct to SD	Comparator	End points	Results	Ref.
Milne *et al.* (2012)	PU (stages III and IV)	Prospective, continuation of Milne 2010	Long-term care facilities	No; continuation of Milne 2010 study	Hydrogel	Maintenance debridement, wound closure with CCO compared versus hydrogel from time of necrotic tissue removal up to 84 days from enrollment Assessed by weekly photographs evaluated with digital planimetry software, PUSH Tool score and WBS	No significant difference between groups in days to healing or complete epithelialization. In aggregated Phase I and Phase II data, closure rates at the end of the study: CCO (69%) and hydrogel (21%; p = 0.0213). At time of complete debridement, 7 patients had stage III PUs (4 CCO; 3 hydrogel), 6 patients had stage IV PUs (6 CCO; 0 hydrogel). Greater severity of stage in CCO group (p = 0.03)	[34]
Carter *et al.* (2016)	PU (stage IV)	Retrospective cohort based on USWR	Hospital outpatient	Yes	SD without CCO	Percent of wounds closed; time to wound closure	The proportion of PU closed at 1 or 2 years: CCO versus control: 22.2% (75/337) versus 11.0% (37/336) at 1 year ($p < 0.0001$) and 26.7% (90/337) versus 13.7% (46/336) at 2 years ($p < 0.0001$), respectively. The mean time to wound closure within 2 years for stage IV CCO-treated PU was 456 days (95% CI: 415.9–496.0) versus 589 days (95% CI: 553.4–624.5; $p < 0.0001$). Kaplan–Meier analysis showed that time to wound closure at 1 year was significantly faster for PU treated with CCO versus PU not treated with CCO	[12]

AD: Autolytic debridement; BWAT: Bates–Jensen Wound Assessment Tool; CCO: Clostridial collagenase ointment; NPWT: Negative-pressure wound therapy; NS: Not significant; PU: Pressure ulcer; PUSH: Pressure Ulcer Scale for Healing; SD: Selective debridement; USWR: United States Wound Registry; WBS: Wound bed score.

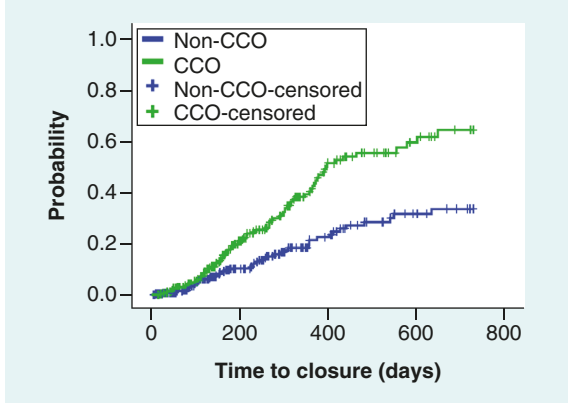

Figure 1. Time to wound closure within 2 years (Kaplan–Meier plot). The + markers indicate where censoring takes place timewise for each of the groups. CCO: Clostridial collagenase ointment. Reproduced with permission from [12] © John Wiley and Sons (2016).

and 26.7% [90/337] vs 13.7% [46/336] at 2 years; $p < 0.0001$, respectively). Kaplan–Meier analysis showed that time to wound closure at 1 year was significantly faster for PU treated with CCO versus PU not treated with CCO (Figure 1).

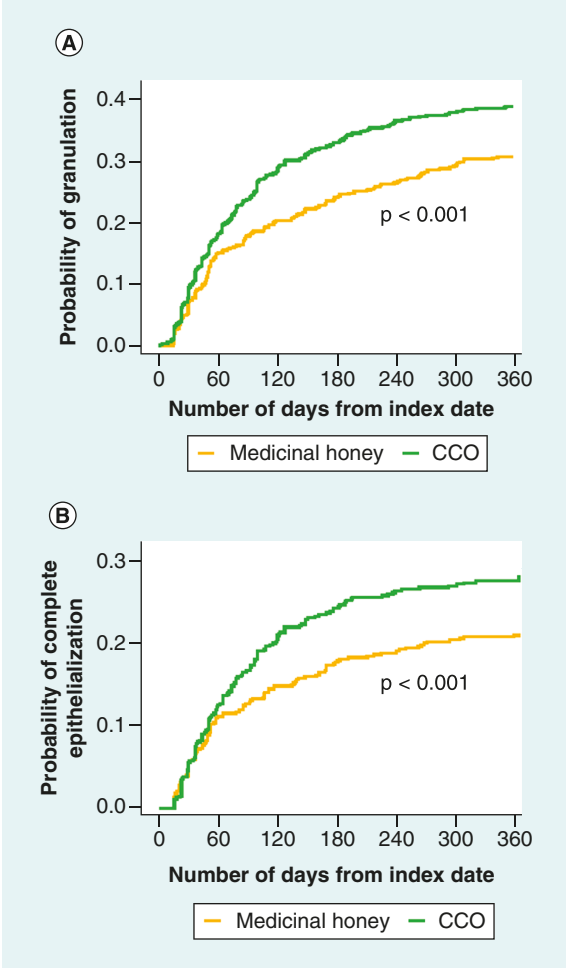

Figure 2. Achievement of key wound closure outcomes with clostridial collagenase ointment versus medicinal honey for treatment of pressure ulcers. (A) Probability of 100% granulation over 365 days (Kaplan–Meier curve). **(B)** Probability of complete epithelialization over 365 days (Kaplan–Meier curve).
CCO: Clostridial collagenase ointment.
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Another analysis utilizing the USWR compared the effectiveness of enzymatic debridement with CCO versus AD with medicinal honey in patients with PU [37]. Among 517 CCO-treated PUs (446 patients) and 517 matched corresponding honey-treated PUs (341 patients), CCO-treated PU were 38% more likely to achieve 100% granulation versus honey-treated PU at 1 year ($p = 0.018$) and 47% ($p = 0.024$) more likely to epithelialize at 1 year compared with honey-treated PU (Figure 2). CCO users also had significantly fewer total visits (9.1 vs 12.6; $p < 0.001$), fewer total selective sharp debridements (2.7 vs 4.4; $p < 0.001$) and fewer PUs requiring negative-pressure wound therapy (NPWT; 29 vs 38%; $p = 0.002$) compared with medicinal honey users.

CCO has also been assessed for PU management in the long-term acute care setting in conjunction with NPWT [38]. In a retrospective cohort study of patients (n = 114) in two long-term acute care hospitals, CCO in conjunction with NPWT demonstrated greater speed of wound healing and reduction of necrotic tissue compared with NPWT alone [38]. Of note, sharp debridement was performed in a subgroup of 41 patients. Analysis of this subgroup indicated that, compared with NPWT and sharp debridement alone, PUs treated with sharp debridement, NPWT and CCO demonstrated statistically significant increases in the rate of debridement (lower necrotic score on Bates–Jensen Wound Assessment Tool items 5 and 6) and the rate of healing (overall reduction in Bates–Jensen Wound Assessment Tool score), suggesting a possible synergistic effect between the use of sharp debridement and CCO for treating PU.

Effectiveness of CCO in debridement of DFU in outpatient settings

CCO has been examined for the treatment of DFUs in several studies in the outpatient setting, as monotherapy versus AD, monotherapy versus mechanical debridement (MD) plus selective sharp debridement or in combination with sharp debridement versus sharp debridement alone (Table 2) [15,39–41].

Table 2. Recent clostridial collagenase ointment trials for debridement of diabetic foot ulcers.

Study (year)	Patient population	Study design	Setting	Adjunct to SD	Comparator	End points	Results	Ref.
Motley *et al.* (2014)	DFU	Prospective, randomized, open-label	Outpatient	Yes	SD without CCO	Percentage change in ulcer area from baseline at the end of the debridement/treatment period (EOT)	Wound area decreased relative to baseline for both the CCO group (-68%, -61%; $p < 0.001$ vs baseline) and the control group (-36%, -46%; p = NS vs baseline) at EOT and EOS, respectively. Intergroup differences did not reach statistical significance	[39]
Tallis *et al.* (2013)	DFU	Prospective, randomized, open-label	Physician office or hospital outpatient	No	SD and MD with saline gauze (after initial SD in both groups)	Condition of the wound bed at EOT; percentage of reduction in wound area and therapeutic response rates	Decrease from baseline in mean wound area: CCO: -44.9%, p = 0.016 at EOT, and -53.8%, p = 0.012 at EOS Results NS for control group CCO group exhibited a significantly better response rate at the end of follow-up versus the SMG group (0.92 vs 0.75 based on WAT modified from BWAT; $p < 0.05$)	[40]
Galperin *et al.* (2015)	DFU	Prospective, randomized, open-label	Outpatient	No	Hydrogel	8-category assessment tool derived from BWAT; wound measurement via ARANTZ Silhouette® digital wound imaging system (Christchurch, New Zealand)	Significant and progressive reduction in mean percentage change from baseline in wound area for CCO for weeks 1 through 4 (-29, -55, -62 and -70%, respectively) Hydrogel: percent change from baseline was significant only at the end of week 1 (-33%)	[15]
Jimenez *et al.* (2017)	DFU	Prospective, randomized, open-label	Outpatient	No	Hydrogel†	Wound area measurement via ARANZ Silhouette digital wound imaging system; visual assessment of granulation	Wound area decreased relative to baseline for both the CCO group (-60%; $p < 0.0001$; -65%; $p < 0.0001$) and the control group (-50%; p = 0.0001; -51%; p = 0.0001) after 6 and 12 weeks, respectively. Intergroup differences at 6 and 12 weeks, NS mean percentage reductions for the CCO group were greater than those for the control at all 12 time points (averages: -55 and -41%, respectively)	[41]

†SD permitted for both groups throughout treatment period at investigators' discretion.
BWAT: Bates–Jensen Wound Assessment Tool; CCO: Clostridial collagenase ointment; DFU: Diabetic foot ulcer; EOS: End of study; EOT: End of treatment; MD: Mechanical debridement; NS: Not significant; SD: Selective debridement; SMG: Saline-moistened gauze; WAT: Wound Assessment Tool.

In a prospective, randomized, open-label trial by Motley *et al.* in patients with DFU, enzymatic debridement with CCO in conjunction with serial sharp debridement demonstrated benefit beyond serial sharp debridement with standard care alone [39]. Wound area was statistically significantly decreased from baseline at both end of treatment (6 weeks) and end of study (12 weeks) in the group receiving both CCO and sharp debridement (n = 28; -68 and -61%, respectively; $p < 0.001$ for both time periods), but not in those receiving only sharp debridement (n = 27; -36 and -46%, respectively). The intergroup difference did not reach statistical significance. On average, ulcers treated with serial sharp debridement plus adjunctive CCO decreased in size more rapidly than ulcers treated without adjunctive CCO debridement, with median time to closure for wounds that healed of 6 weeks for CCO and 8 weeks for control.

Similar CCO benefit was observed in another prospective, randomized, open-label trial comparing CCO monotherapy (n = 24) with a combined therapy of MD (saline-moistened gauze [SMG]) plus selective sharp debridement (n = 24). Only CCO treatment resulted in a statistically significant decrease from baseline in the mean

Table 3. Recent clostridial collagenase ointment trials for debridement of venous leg ulcers.

Study (year)	Patient population	Study design	Setting	Adjunct to SD	Comparator	End points	Results	Ref.
Gilligan *et al.* (2015)	VLU	Retrospective review based on USWR	Hospital outpatient	No	AD with honey	Clinical improvement	Wound closure rates: CCO: 45%; medicinal honey: 31%	[42]
Gilligan *et al.* (2015)	VLU	Retrospective review based on USWR	Hospital outpatient	No	AD with undifferentiated wound dressings alone	Clinical improvement	CCO demonstrated greater clinical improvement than VLU treated with undifferentiated wound dressings (no specific results provided)	[43]

AD: Autolytic debridement; CCO: Clostridial collagenase ointment; SD: Selective debridement; USWR: United States Wound Registry; VLU: Venous leg ulcer.

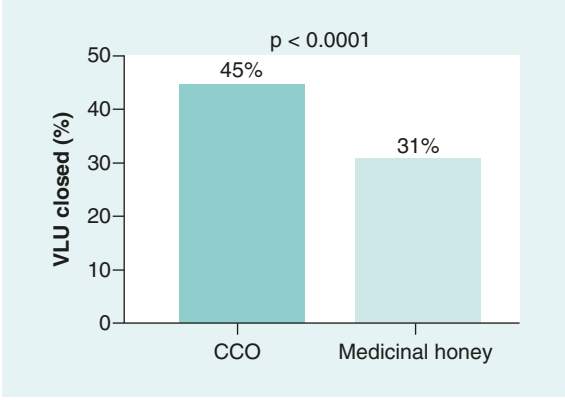

Figure 3. Percentage of venous leg ulcers documented as closed by end of treatment.
CCO: Clostridial collagenase ointment; VLU: Venous leg ulcer.

wound area at the end of treatment (-44.9%; p = 0.0164) and at the end of follow-up (-53.8%; p = 0.012) [40]. Corresponding changes for the SMG group were +0.8 and +8.1%.

Jimenez *et al.* recently assessed outcomes associated with use of CCO in patients with diabetes and DFU in a prospective, randomized, open-label study of 215 patients [41]. All patients received sharp surgical debridement at baseline, then were randomized to receive CCO (n = 106) or standard care (hydrogel daily as needed to maintain wound moisture; n = 109). Sharp debridement was permitted for both treatment groups at the investigators' discretion. Wound area decreased relative to baseline for both the CCO group (-60%; p < 0.0001 and -65%; p < 0.0001) and the control group (-50%; p = 0.0001 and -51%; p = 0.0001) after 6 and 12 weeks, respectively. While intergroup differences at 6 and 12 weeks did not reach statistical significance, mean percentage reductions in wound area were greater for the CCO group than the control group at all 12 time points (averages: -55 and -41%, respectively). Of note, DFUs that showed no improvement at 4 weeks (n = 24; 12/group) were crossed over to the other treatment group. A numerically greater proportion of subjects who switched to CCO achieved closure (33%) than did those who switched to standard care (8%).

Effectiveness of CCO in debridement of VLUs

Two retrospective cohort studies based on EHRs (2007–2013) of over 9000 patients with VLUs from the USWR demonstrated that VLUs treated with CCO were significantly more likely to improve (i.e., reduced wound surface area) relative to those treated with undifferentiated wound dressings alone (p < 0.05), and significantly more likely to achieve 100% granulation and to epithelialize by the end of therapy compared with wounds treated with medicinal honey (30 vs 19%, respectively, for granulation; p < 0.01 and 45 vs 31%, respectively, for epithelialization; p < 0.0001; Table 3 & Figure 3) [42,43].

Effectiveness of CCO in debridement of burns

The effectiveness of CCO in burn treatment has been demonstrated in several studies compared with surgical excision, silver sulfadiazine or MD, in both the hospital and outpatient burn center (Table 4) [25,29,44–45]. Hansbrough *et al.* conducted a trial in 79 patients (age range: 5–60 years) with partial-thickness burn wounds in which paired wound sites of comparable size and severity in each patient were randomized to treatment with either CCO

Table 4. Recent clostridial collagenase ointment trials for debridement of burns.

Study (year)	Patient population	Study design	Setting	Adjunct to SD	Comparator	End points	Results	Ref.
Frye and Luterman (2005)	Burns	Retrospective review	Outpatient burn center	No	MD (WTD)	Hypertrophic scar formation	Saline WTD group: 46 (20.4%) patients developed significant scar postclosure of the wounds. CCO group: 19 (9.2%) patients; $p < 0.001$	[44]
Hansbrough *et al.* (1995)	Burns	Prospective	Hospital	No	Silver sulfadiazine	Time to clean wound bed; time to epithelialization	Comparison of paired treatment sites within each patient: wound cleaned first in 47 versus 12% of CCO- and silver sulfadiazine-treated wounds, respectively ($p < 0.001$). Wound healed first in 42 versus 8% of CCO- and silver sulfadiazine-treated wounds, respectively ($p < 0.001$). Numerically faster time to clean wound bed (9.3 vs 11.6 days), and for CCO versus silver and faster epithelialization (19 vs 22.1 days) for CCO sites versus silver sulfadiazine sites	[25]
Ostlie *et al.* (2012)	Burns	Prospective, randomized in children	Hospital	No	Silver sulfadiazine	Primary outcome was the need for skin grafting	No difference in need for grafting	[29]
Ozcan *et al.* (2002)	Burns	Prospective, in children	Hospital	No	Surgical excision	Time to achieve a clean wound bed, requirement for blood transfusions, number of excisions per patient, number of patients necessitating tangential excision and/or grafting, wound infections and length of hospital stays	No significant difference in the time to achieve a clean wound bed; hospital stay shorter in CCO group (12.5 vs 20 days; $p < 0.01$)	[45]

CCO: Clostridial collagenase ointment; MD: Mechanical debridement; SD: Selective debridement; WTD: Wet to dry.

with polymyxin B sulfate/bacitracin powder or silver sulfadiazine. Comparison of paired treatment sites within each patient demonstrated that proportionally more CCO-treated sites were cleaned ($p < 0.001$) and healed ($p < 0.001$) before similar sites treated with silver sulfadiazine. Time to clean wound bed (mean: 9.3 vs 11.6 days) and time to epithelialization (mean: 19.0 vs 22.1 days) were both numerically faster in sites treated with CCO compared with those treated with silver sulfadiazine, but the difference did not reach statistical significance [25].

Another prospective, randomized trial comparing CCO/polymyxin with silver sulfadiazine performed in 100 children with partial-thickness burns found no differences in outcomes in skin graft rates, length of stay and hospital costs between treatment groups [29]. The similarities in overall costs between treatment groups support the finding that the more significant charges of hospital room, treatment room times and operative interventions far outweigh the minimal difference in topical agent expense, so that agent choice should not be determined by agent cost [29].

In a prospective study in 119 children with partial-thickness burns, the use of CCO shortened the hospital stay and reduced the overall need for surgery and blood transfusions [45]. In 78 patients, treatment was initiated with CCO, and in 41 patients (Group S), burn wounds (of similar surface area and wound depth to those treated with CCO) were surgically excised. In 49 of the 78 patients treated with CCO, total removal of eschar was accomplished with CCO alone (this responsive group was Group D). Among the remaining 29 who had initiated treatment with CCO (Group DS), CCO was terminated because of burn wound infection (n = 17) or a manifest need for wound grafting (n = 12). There was no significant difference between the time to achieve a clean wound bed among the three treatment groups (mean: 7.8, 8 and 7 days for Groups D, DS and S, respectively; $p > 0.05$). Blood transfusion was required in only 1/49 (2%) patients in Group D, compared with 18/29 (62%) patients in Group DS and 30/41 (73%) patients in Group S ($p < 0.01$ for Group D vs either of the other groups). Mean hospital stay was

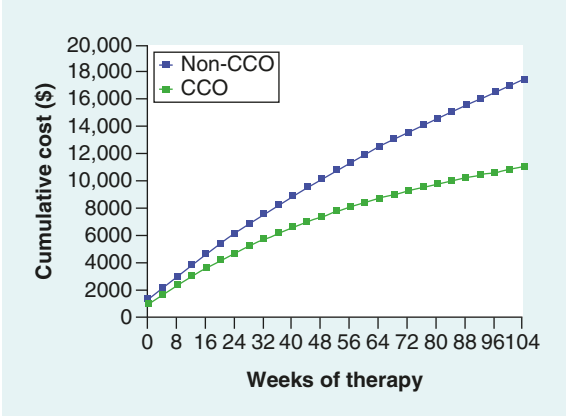

Figure 4. Cumulative costs with clostridial collagenase ointment added to selective debridement and selective debridement alone (non-clostridial collagenase ointment) over the 2-year period in patients with stage IV pressure ulcers.
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shortest for Group D (mean 12.5 days; $p < 0.01$) compared with Group DS (20.7 days) and Group S (20.2 days). The results of these studies suggest that CCO should be considered as the initial treatment of choice for removal of eschar in patients with a partial-thickness burn wound without infection.

CCO for continuous debridement

As demonstrated in several studies discussed above [38,39], CCO is effective either alone or in conjunction with sharp debridement, providing synergistic effects when combined with the latter. An area of more limited study is the effectiveness of CCO in continuous debridement, which is a therapeutic intervention to address the problem of chronic wound beds with absent or slow healing despite appearing to be free from necrotic tissue [34,46]. The chronic wound contains a number of microbial, biochemical and cellular features and abnormalities that prevent or slow its progression to healing despite a seemingly adequate wound bed by appearance [46]. As noted earlier, CCO can potentiate cellular responses vital to wound epithelialization, such as proliferation and migration of keratinocytes and fibroblasts, while decreasing levels of analytes associated with inflammation [15]. As such, it may facilitate wound closure, as demonstrated in the trial by Milne *et al.* in which continuous debridement with CCO in institutionalized adults with PU resulted in superior wound closure rates from time of necrotic tissue removal to 84 days from enrollment [34].

Discussion of economic analyses

The cost–effectiveness of CCO has been studied for almost two decades. Several early models of debridement methods for treatment of chronic wounds deemed CCO to be the least expensive treatment among the treatment strategies that were compared (autolysis, calcium alginate, wet-to-dry dressings, hydrocolloid dressings and fibrinolysin) [47–49].

Cost–effectiveness of CCO in PU

Among models assessing PU patients, debridement with CCO is the economically dominant wound care strategy compared with other treatment strategies (Table 5). Carter *et al.* assessed the cost–effectiveness (from a US payer's perspective; 2015 USD) of adding CCO to selective debridement compared with selective debridement alone (non-CCO) in the treatment of stage IV PU [50]. Outcome data were derived from retrospective deidentified EMRs of patients with stage IV PU from 2007 to 2013 using the USWR [12]. The analysis constructed a three-state Markov model over a 2-year time horizon [50]. Compared with the non-CCO group, CCO incurred lower costs (US$11,151 vs US$17,596) and greater clinical benefit (33.9 vs 16.8 ulcer-free weeks), resulting in an economically dominant treatment option (Figure 4). Over a 2-year period, an additional 17.2 ulcer-free weeks could be gained with a concurrent cost saving of US$6445 for each patient.

A similarly designed study by Mearns *et al.* assessed the cost–effectiveness of enzymatic debridement with CCO compared with autolytic treatment with medicinal honey for stage III or IV PU treatment [52]. A Markov model from a US payer perspective (2016 USD) was developed with a base-case of adult patients with PUs treated in a hospital outpatient department. The three health states in the model included inflammation/senescence, granulation/proliferation (patients achieving 100% granulation) and epithelialization, and were based on observed rates from an analysis of patients from the USWR [37]. CCO was the economically dominant strategy, resulting in

Table 5. Economic analyses of clostridial collagenase ointment for enzymatic debridement.

Study (year)	Patient population	Study design	Setting	Adjunct to SD	Comparator	Costing year, currency	Time horizon	End points	Results[†]	Ref.
Carter *et al.* (2016)	PU	CEA/Markov model	Hospital outpatient	Yes	SD without CCO	2015, USD	2 years	Cumulative costs, ulcer-free weeks, ICERs	ICER for CCO: -US$375 per ulcer	[50]
Dreyfus *et al.* (2017)	PU	Observational database healthcare utilization study	Hospital inpatient and outpatient	Not specified	Medicinal honey	2015, USD	6 months	Frequency of inpatient and outpatient revisits up to 6 months after index encounter for CCO versus medicinal honey treatment	Odds for inpatient re-admissions (OR: 1.16; 95% CI: 1.07–1.25) after inpatient index visits, and odds of outpatient re-encounters after inpatient (OR: 1.37; 95% CI: 1.26–1.48) and outpatient (OR: 1.28; 95% CI 1.05–1.57) index visit greats were greater for medicinal honey	[51]
Mearns *et al.* (2017)	PU	CEA/Markov model	Hospital outpatient	No	AD with medicinal honey	2016, USD	1 year	Cumulative costs, number of granulation and epithelialized weeks, number of clinic visits and debridements, QALWs, ICERs	CCO: 22.7 QALWs at a cost of US$6161 Medicinal honey: 21.9 QALWs at a cost of US$7149	[52]
Motley *et al.* (2015)	DFU	CEA alongside an open-label RCT (NCT 01408277)	Outpatient	Yes; SSD + CCO	SSD + investigator-selected supportive care (silver dressings and hydrogels)	2013, USD	1 year	Number of epithelialized weeks, cost per DFU, cost per ulcer-free week	Cost per ulcer-free week: US$61 for CCO + SSD versus US$85 for control	[53]
Tallis *et al.* (2013)	DFU	CEA alongside an open-label RCT (NCT 01056198)	Physician office or hospital outpatient	No; surgical debridement + CCO	Surgical debridement + SMG	N/R, USD	12 weeks	Cost per responder, wound bed condition, percentage of reduction in wound area and therapeutic response rates, tolerability	Direct mean cost per responder in a physician office was US$832 versus US$1042 for CCO versus SMG; in hospital outpatient setting, US$1607 versus US$1980	[40]
Waycaster and Milne (2013)	PU	CEA	Long-term care facilities	No	Hydrogel	N/R, USD	42 days	Number of granulated wound bed days, cost per patient, ICERs	42-day results: ICER: CCO: + US$12/granulation day average CER: CCO: US$78/granulation day; hydrogel: US$249/granulation day 84-day results: average CER: CCO: US$6/closed-wound day; hydrogel: US$25/closed-wound day	[9,54]

[†]See text for details of other results.

AD: Autolytic debridement; CCO: Clostridial collagenase ointment; CEA: Cost–effectiveness analysis; CER: Cost–effectiveness ratio; DFU: Diabetic foot ulcer; ICER: Incremental cost–effectiveness ratio; N/R, Not reported; OR: Odds ratio; PU: Pressure ulcer; QALW: Quality-adjusted life week; RCT: Randomized controlled trial; SD: Sharp debridement; SMG: Saline-moistened gauze; SSD: Serial sharp debridement; USD: United States dollar.

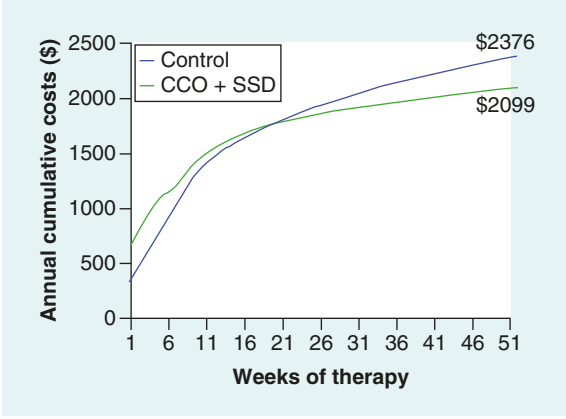

Figure 5. Cumulative costs for clostridial collagenase ointment + serial sharp debridement and control (investigator-selected supportive care + serial sharp debridement) treatments.
CCO: Clostridial collagenase ointment; SSD: Serial sharp debridement.
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22.7 quality-adjusted life weeks at a cost of US$6161 over 1 year, compared with 21.9 quality-adjusted life weeks at a cost of US$7149 for medicinal honey.

Waycaster *et al.* analyzed the cost–effectiveness of CCO versus AD with a hydrogel dressing using clinical and resource utilization data derived from a US-based, prospective, randomized, two-phase trial [9,54]. Patients were residents of a long-term care center and had stages III and IV PUs with ≥85% necrotic nonviable tissue. In the analysis of Phase I (42-day end point), the average cost per patient for 42 days of PU care in 2012 was US$1817 for CCO and US$1611 for hydrogel, but days spent with a granulated wound were 3.6 times higher with CCO (23.4 vs 6.5) than hydrogel [54]. The incremental cost–effectiveness ratio was US$12, yielding an estimated cost per granulation day more than 3.2 times higher for hydrogel (US$249) versus CCO (US$78). At the end of Phase II of this study, direct cost per patient for PU care was US$2003 for CCO and $5480 for hydrogel, and the number of closed wound days was 1.5 times higher with CCO than hydrogel (317 vs 218 days) [9]. The estimated cost–effectiveness ratio was $6/closed-wound day for CCO and US$25/closed-wound day for hydrogel, indicating a fourfold higher cost per PU-free day for hydrogel versus CCO. These findings demonstrate economic dominance of CCO debridement over AD with hydrogel, which occurs when CCO is both clinically superior and cost effective.

Cost–effectiveness of CCO in DFU

Two cost analyses of CCO debridement in patients with DFU also yielded estimates favoring CCO over alternative debridement methods [40,53]. In an analysis of results from a randomized, open-label trial of 55 patients with DFU using a three-state Markov model, Motley *et al.* calculated that the number of epithelialized weeks was 25% greater in patients treated with the CCO plus serial sharp debridement (35 weeks) versus other debridement methods (28 weeks) [39,53]. Using a 1-year time horizon from a third-party payer perspective, the expected cost per treated DFU was greater for standard DFU care plus serial sharp debridement compared with CCO plus serial sharp debridement: 2376 versus US$2099, respectively (Figure 5). Cost per ulcer-free week was 40% higher for standard DFU care plus serial sharp debridement versus CCO plus serial sharp debridement (85 vs US$61 per closed-wound week).

Tallis *et al.* [40] conducted an economic analysis alongside a multicenter, open-label, 12-week RCT of 48 patients with DFU treated with either CCO or SMG after baseline surgical debridement (with further surgical debridement as deemed necessary in either group). Resource use estimates included frequency of selective sharp debridement procedures between groups (mean of 1 and 7 for CCO and SMG groups during the trial, respectively) and physician office visits (6 and 12 during the trial, for CCO and SMG groups, respectively) associated with the evaluation and management of patients with DFU and CCO use. Response rates were categorized as follows: large response (ulcer area reduction from baseline ≥50%), moderate response (ulcer area reduction from baseline <50% but >10%) or stalled response (ulcer area reduction from baseline ≤10%, or increase in size). Direct mean cost per responder for CCO versus SMG was 832 versus US$1042 in the physician office setting and 1607 versus US$1980 in the hospital outpatient setting.

Health resource utilization of CCO

Recently, Dreyfus *et al.* analyzed the impact of CCO compared with medicinal honey on healthcare utilization among patients with PU in real-world inpatient and outpatient hospital settings [51]. Hospital discharge records

(from 2000 to 2016) of patients receiving debridement with an International Classification of Diseases – ninth edition code for PU were extracted from the US Premier Healthcare Database, which contains data from more than 646 million patient encounters (~1 in every 5 discharges in the nation). The frequency of inpatient and outpatient revisits up to 6 months after an index encounter for CCO-treated PU versus medicinal honey-treated PU was compared with multivariate analysis. Among inpatients, n = 44,725 (60% of discharges) were treated with CCO and n = 3542 (5%) with medicinal honey. Among outpatients, n = 1826 (7%) and n = 773 (3%), respectively, were treated with CCO and medicinal honey. In adjusted models, those treated with medicinal honey had greater odds for inpatient re-admissions (odds ratio [OR]: 1.16; 95% CI: 1.07–1.25) after inpatient index visits, and greater odds for outpatient re-encounters both after inpatient (OR: 1.37; 95% CI: 1.26–1.48) and outpatient (OR: 1.28; 95% CI: 1.05–1.57) index visits during 6 months of follow-up.

Conclusion

As demonstrated by the results of clinical trials and real-world data discussed above, CCO is effective for the debridement of all chronic wounds and burns, and across multiple care settings. Unlike other modalities of debridement, CCO debridement can be used in most patients and can be performed in any care setting, by any caregiver. As such, CCO is an ideal choice both for initial debridement (either alone or in conjunction with initial and/or serial sharp debridement) as well as for continuous debridement. These qualities make CCO suitable for use across the continuum of settings and transitions in wound care patients, from hospital to short-term care facility to home. In addition to its effectiveness when used as monotherapy for debridement, the addition of CCO to selective sharp debridement or to NPWT improves outcomes over either of those modalities used in isolation. All the economic studies of patients with PU and DFU have demonstrated the cost–effectiveness of CCO compared with other treatment strategies. Patients treated with CCO had fewer outpatient re-encounters, fewer clinic visits and debridements and faster rates of epithelialization, all of which translate into cost savings.

Future perspective

Currently, complete wound healing (i.e., skin re-epithelialization without drainage or dressing requirements) is the only FDA-approved 'hard' clinical trial end point to demonstrate efficacy for wound treatment products [55]. Consequently, there are no currently FDA-approved end points that might be more suitable for short-term outcomes, such as wound granulation percentage at 4 weeks after first or last CCO application. A group of wound care researchers is currently working with the FDA to approve new clinical-reported outcome and patient-reported outcome end points that may be more suitable end points for clinical trials involving CCO [56].

The USWR is a Qualified Clinical Data Registry (QCDR), a reporting mechanism by which providers participate in the Merit-Based Incentive Payment System. A QCDR is a US Centers for Medicaid and Medicare Services (CMS)-approved entity that collects medical and/or clinical data for the purpose of improving the quality of care furnished to patients. Quality data submitted to a QCDR must include patients across all payers and is not limited to Medicare beneficiaries. Importantly, QCDRs can develop quality measures relevant to a specialty or patient population as the USWR has done for wound care. Quality measures are an increasingly important part of many Medicare payment systems including those for acute care hospitals, long-term care, nursing homes and hospital-based outpatient departments [57]. Patients with chronic wounds are commonly treated in all of these settings; therefore, the near-absence of available wound care quality measures threatens both quality of patient care and reimbursement for wound care services. Among all of these settings, there is only one measure relevant to wound care and that is the counting and staging of pressure ulcers. The only other relevant wound care quality measures are those that practitioners can report through the QCDR. In 2014, the USWR developed a wound debridement quality measure for which it was able to establish a 'benchmark rate' in 2016 of 69.8%. Unfortunately, in 2017 this measure was rejected by CMS based on the argument that the high passing rate of the reporting physicians proved a 'gap in practice' that no longer existed with regard to debridement. It should be noted that among practitioners not reporting this measure to CMS the passing rate was low. In any case, physicians no longer have a debridement quality measure to inspire best practices in this aspect of wound care. Physicians could satisfy the measure using any method of debridement (e.g., sharp, autolytic, biologic, CCO, etc.) and could thus select the method most appropriate to the clinical situation. Many factors affect the use of CCO. For example, CCO is the only drug in its class, and it has an evidence base demonstrating cost–effectiveness and clinical effectiveness for the debridement of all chronic wounds and burns across multiple care settings. Yet, CCO is considered a tier 3 or tier 4 treatment in

outpatient settings for purposes of reimbursement, creating a barrier to approval and reimbursement by payers for its use in wound care.

The European Wound Management Association has produced several documents providing guidance on how to improve evaluations of new treatment strategies regarding outcome measures in both RCTs and clinical studies that will meet the requirements for evidence-based information in wound management [58–60]. Hopefully, these guidance documents will contribute to the development of universal standards for outcome measures within the next 5 years and result in more comparative effectiveness studies that will be the basis for reimbursement of wound care therapies.

Executive summary

Background

- The prevalence of chronic dermal ulcers is increasing in light of the aging of the population, and such wounds are associated with loss of function, decreased quality of life and significant direct and indirect costs.
- Debridement is a critical component of wound care involving removal of nonviable tissue from chronic wounds to stimulate the wound granulation and epithelialization process.
- Clostridial collagenase ointment (CCO) is currently the only enzymatic debriding ointment with US FDA approval.
- Experimental data suggest that, in addition to its debriding activity, CCO may actively promote healing by potentiating cellular migratory, proliferative and angiogenic responses to injury. Further, CCO may decrease the excessive and prolonged inflammation associated with nonhealing wounds by downregulating inflammatory cytokines.

Discussion of clinical effectiveness

- The effectiveness of CCO for debridement of diabetic foot ulcers, pressure ulcers and venous leg ulcers, as well as burns, has been demonstrated by a number of clinical trials across multiple care settings (i.e., hospital inpatient, outpatient and long-term care facility).
- Several of the studies utilize real-world data from the US Wound Registry. These studies may be more generalizable to clinical practice compared with analyses based on controlled clinical trials, as the registry includes typical patients often excluded from randomized controlled trials and reflects actual practice.
- CCO has demonstrated clinical effectiveness both alone and in conjunction with sharp debridement, providing synergistic effects when combined with the latter.

Discussion of economic evaluation/burden

- Multiple analyses have demonstrated the cost–effectiveness and cost savings, and in some cases, economic dominance of CCO for the management of chronic wounds.
- Comparator methods of debridement in these analyses included autolysis with medicinal honey or hydrogel dressing, moistened saline dressing and monotherapy with sharp debridement (compared with addition of CCO to sharp debridement).
- Patients treated with CCO had fewer outpatient re-encounters, fewer clinic visits and debridements and spent more weeks in epithelialization, all of which translates into cost savings.

Conclusion

- CCO is effective for the debridement of all chronic wounds and burns, and across multiple care settings, both as monotherapy and in conjunction with selective sharp debridement.
- CCO has demonstrated cost–effectiveness, and in some cases, shown economic dominance compared with other strategies in the treatment and management of chronic wounds.

Financial & competing interests disclosure

C Waycaster is an employee of Smith & Nephew and may own shares of Smith & Nephew. MJ Carter is a consultant to Smith & Nephew. AM Gilligan is a consultant to Smith & Nephew. ES Mearns is a consultant to Smith & Nephew. CE Fife is a consultant to Smith & Nephew. CT Milne is on the speakers' bureau for Smith & Nephew. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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