An Overview of Clinical and Health Economic Evidence Regarding Porcine Small Intestine Submucosa Extracellular Matrix in the Management of Chronic Wounds and Burns

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Abstract

Small intestine submucosa (SIS) has been extensively evaluated in preclinical models and developed into commercially produced medical technologies intended for use in several different indications. The SIS extracellular matrix cellular and/or tissue-based product is a commercially available, porcine-derived SIS dressing. The purpose of this review was to consider the role of the SIS dressing in the management of chronic wounds and burns. Using a variety of search terms from the literature to describe the SIS dressing, the following databases were searched: PubMed, York Centre for Reviews and Dissemination database, National Health Service Economic Evaluation database, Health Technology Assessment database, and the Cochrane Library. The search identified 78 studies of which 21 met the inclusion/exclusion criteria. Of those, 14 involved chronic wounds, 3 described the management of burn wounds, and 4 were economic evaluations. The wide variety of comparative treatments and outcomes studied precluded the use of meta-analysis techniques. Study results show SIS dressings may improve outcomes in chronic wounds and cost less than several alternative biological wound treatments. Studies to examine their efficacy in burn wound management are warranted.

Keywords: wound healing, porcine small intestine submucosa, extracellular matrix, chronic wounds, burns

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A wound survey conducted by Vowden et al[1] in 2 local health authorities in the United Kingdom found wounds of various causes in all types of health care settings from acute care facilities to long-term institutions contribute substantially to the costs of hospitalization and nursing time. Similarly, Posnett et al[2] considered the cost and impact of chronic wounds on patients and health care systems in the UK and also reviewed evidence on prevalence and costs of chronic wounds in the European Union[3]; the authors concluded chronic wounds are a hidden but significant health care burden. In the European Union alone, 1.5 to 2.0 million individuals receive regular wound care from a health care professional at any one time.[3] In addition to their economic burden, wounds also cause substantial pain and distress to patients. A systematic review[4] that included 37 studies examining the impact of leg ulcers on quality of life noted patients were concerned about pain. A prospective study[5] that included 10 patients living with wounds and a cross-sectional study[6] among 73 patients found wounds had a negative impact on quality of life and that appropriate services should be designed to take into account patients' needs. Furthermore, with an aging population and increasing rates of chronic conditions such as diabetes and obesity, the incidence of wounds is expected to increase. In light of these factors, there is a continual need to improve the efficiency of wound care services and to consider the role of technologies that accelerate wound resolution and, consequently, optimize patient outcomes.[2] However, the desire to use promising, novel technologies needs to be counterbalanced against the need to make the best use of scarce budgets.

The majority of chronic wounds are comprised of venous leg ulcers (VLUs), pressure ulcers (PUs), and diabetic foot ulcers (DFUs). VLUs account for 40% to 70% of chronic lower extremity wounds.[6] A review of the evidence and costs of diabetes ulceration[7] noted DFUs are a common complication in

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diabetes and the largest contributor of morbidity in diabetic neuropathy. PUs are a frequent and predominantly age-related occurrence for bedridden patients in hospitals and institutions; severe ulcers (those that extend beyond the skin into muscle, tendon, and bone) pose a particularly high risk of infection and mortality.[2] EUCOMED[8] recently underscored the burden of wounds by reiterating that between 25% and 50% of acute hospital beds are occupied by patients with either acute or chronic wounds.[3] A prospective observational study in Spain[9] found wounds are a large contributor to the incidence of nosocomial infections and other complications related to hospitalization among hospitalized elderly patients.

Burn injuries also pose a significant challenge to wound care providers. Extensive and/or deep burns have been shown in a meta-analysis[10] of observational and randomized controlled trials to be more difficult to manage, often requiring lengthy hospitalization and complex treatments; these complex burns also are associated with a significant risk of complication that can result in a protracted healing process. According to the Expert Working Group International Best Practice Guidelines on management of noncomplex burns,[11] a decline in the severity and incidence of burn injuries in Europe during the last 2 decades is attributed to enhanced public awareness and prevention strategies that facilitated management of many burns outside of specialist burn units. However, a cross-sectional cohort study[12] of burn patients presenting for formal treatment at 2 UK city hospitals over a 10-year period identified a relatively high proportion of burn victims (up to 11%) are admitted to specialist burn units. In addition, the study revealed that over this same time frame, there was a total incidence of 4577 cases of second-degree and third-degree burn presentations and improvements in predicted mortality. A retrospective review[13] of patients with thermal injuries admitted to a single center in a German hospital considered treatment of burns in 2 different decades (1991–2000 [911 patients] and 2001-2010 [695 patients]); it concluded the severity of burns has declined, probably due to the effectiveness of prevention campaigns.

According to *in vivo*, *in vitro*, and clinical studies,[14,15] porcine small intestine submucosa (SIS) extracellular matrix contains critical components considered key in supporting granulation and epithelialization in dermal wounds and providing a scaffold for tissue repair such as collagen, proteoglycans, and growth factors. SIS is commercially available in biological dressings designed to mimic the human cutaneous natural extracellular matrix and initially received regulatory clearance in August 1997; it is currently available for sale in the United States, Canada, Mexico, Europe, and Australia.[16,17] SIS is indicated for the management of acute and chronic and partial-thickness and full-thickness wounds; multiple variants are available, comprising 1, 2, and 3 layers for various indications. The product is supplied in a freeze-dried, sterile form, has a shelf life of 24 months, and is currently available in 4 sizes ranging from 10.5 cm^2 to 140 cm^2.

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Key Points

- The authors conducted a nonsystematic review of available literature to consider the potential role and costs of using porcine small intestine submucosa (SIS) extracellular matrix dressings in the management of patients with chronic wounds or burn injuries.
- Results suggest the SIS dressing is effective in the management of chronic wounds and less costly than several other biologic wound treatment modalities.
- Evidence about the effectiveness of SIS in burn wound management is promising but very limited.
- Carefully controlled clinical studies are needed to further examine the efficacy of SIS compared to non-biologic and biologic treatment modalities.

Since the first SIS dressings became commercially available, a growing body of evidence has been established on their clinical value in the treatment of chronic wounds; this includes a systematic review[18] that examined dressings, including growth factors, used in VLUs; a nonsystematic review[19] that assessed a variety of SIS extracellular matrix technology in hard-to-heal wounds; and a Health Technology Assessment (HTA) report[20] that assessed all skin substitutes used in chronic wounds. These studies concluded that in patients with chronic wounds for whom standard treatment has been unsuccessful, the use of adjunctive therapies, such as SIS and other growth factors, may improve outcomes in the long term.

More recently, clinical evidence from observational studies and case series[21-23] has begun to emerge on the applicability of SIS dressings to burns. Similar in all other ways, SIS specifically for burns is produced as 2 layers to maximize infection control and minimize fluid loss, potential complications specific to burns.

No reviews have been published of either the clinical and economic evidence showing SIS can maximize infection control and minimize fluid loss or on potential complications specific to burns that have been treated with SIS dressings. Given the scarcity of health care resources, it is important that clinical outcomes are considered along with evidence on the economic value of new technologies. Thus, the purpose of this nonsystematic review was to consider the role of an advanced cellular and/or tissue-based product (CTP) — specifically, porcine SIS (OASIS™ Extracellular Matrix; HealthPoint, Ltd, Fort Worth, TX) — in the management of chronic wounds and burns.

Although individual studies have been reported, no concerted attempt has been made to collate all the published clinical and cost-effectiveness evidence on porcine SIS in the management of wounds.

Methods

This review is based on a nonsystematic, top-level keyword search in PubMed, University of York Centre for Reviews and Dissemination (CRD) databases (ie, National Health Service Economic Evaluation Database and HTA) and the Cochrane Library up to July 2016; an update search was run in April 2017. The search was not limited by date. Search terms were determined by index: the search terms used in PubMed were *OASIS® WOUND matrix* or *OASIS® WOUND healing, porcine small intestine submucosa (SIS)*, and *extracellular matrix*; *OASIS* was used for the CRD database; and *OASIS® wound matrix* was used for the Cochrane Library. In addition, the reference lists of identified systematic reviews or published HTA reports were hand-searched for references. All studies reporting clinical and cost-effectiveness evidence in chronic wounds and burns were included in the review. The intervention had to be SIS compared to standard care, which could be any of the advanced wound care dressings. Laboratory and animal studies were excluded. One author assessed the abstracts and full texts of studies identified from the search following a discussion of the inclusion criteria. Data on the population (ie, all patients with chronic wounds or burns treated with SIS) and its comparators, authors, and year of publication, outcomes such as healing, length of hospital stay, epithelialization, and costs were abstracted and are presented in Table 1.

Results

Search results. The search identified 78 studies, 21 of which addressed SIS in wound management and were included in the nonsystematic review (see Table 1). The 21 comprised 6 randomized controlled trials (RCTs)[16,17,24-27] and 8 observational studies in chronic wounds.[28-35] Three (3) studies involved burns[21-23] and 4 were economic evaluations[36-39] that compared SIS to conventional dressings as well as newer medical devices. The observational study by Martinson and Martinson[29] also reported on economic endpoints.

Clinical evidence on SIS dressings in chronic wounds: clinical and patient outcomes. Wound closure is typically the preferred endpoint in trials of treatments for chronic wounds[20]; it is measured as the rate of or time to complete wound closure, defined as full epithelialization with no drainage.[16,17,25] In the studies reviewed, SIS as an adjunct to compression therapy dressings achieved statistically significant ($P \leq .05$) enhanced rates of healing compared with compression therapy alone (55% versus 34%, respectively),[16] moist gauze (80% and 65%, respectively),[17] and hyaluronic dressings (82.6% versus 46.3%, respectively)[25] in VLUs and compared with becaplermin wound gel (Regranex◊; Smith & Nephew, Fort Worth, TX), 49% versus 28%, respectively,[26] in DFUs. However, no difference was observed by Landsman[24] for SIS dressings compared with living skin equivalent (LSE; Dermagraft®; Organogenesis, Canton, MA) in DFUs. A recent RCT[27] in patients with DFUs found a statistically significant difference in wound closure between SIS and standard care as selected by the study investigator, including silver dressings, hydrogel, wet-to-dry wound dressings, or triple antibiotic dressings (54% versus 32%, $P = .021$). A retrospective study[29] using claims data from the Centers for Medicare and Medicaid Services (CMS) Standard Analytical Files (SAF) between January 2011 and December 2014 from DFU patients (13 193 skin substitute treatment episodes) also found SIS was less expensive than its comparators and more wounds were healed at 90 days.

Other reported outcomes observed for SIS in chronic wounds relative to other active treatment modalities observed in RCTs and observational studies included fewer dressing changes in VLUs and DFUs,[16,17,25] fewer re-hospitalizations in VLUs,[16] and improved pain and comfort per Visual Analog Scale scores for VLUs.[25] SIS has been observed to be well tolerated and easy to apply,[31] facilitate grafting,[28,30] and improve quality of life.[31]

Cost effectiveness evidence in chronic wounds. Five (5) published studies compared the cost effectiveness of SIS dressings with active treatments or best supportive care in chronic wounds: 2 involved patients with VLUs[36,37] and 3 considered patients with DFUs.[29,38,39] Martinson and Martinson[29] conducted a retrospective database analysis using data from the CMS SAF collected between 2011 and 2014 in patients with DFUs that analyzed 13 193 skin substitute treatment episodes comparing human skin equivalent (HSE) (Apligraf®; Organogenesis) (4926, 37.3%), LSE (5530, 41.9%), SIS (2458, 18.6%), and MatriStem® Urinary Bladder Matrix (UBM; ACell Inc, Columbia, MD) (279, 2.1%). The authors found that on average the mean application was 5.5 times per episode of DFU and the percentage of wounds that healed at 90 days was 63% for SIS, 62% for UBM, and 58% each for HSE and LSE. Mean cost (standard deviation) per episode was estimated to be \$1901 ± \$5394 for SIS, \$1435 ± \$3160 for UBM, \$5364 ± \$6966 for HSE, and \$14 424 ± \$15 074 for LSE. Using SIS resulted in higher healing rates and was a less-expensive option compared to HSE and LSE and is therefore considered a dominant strategy.

Hankin et al[36] considered the number needed to treat (NNT) to achieve 1 additional treatment success (defined as wound closure) in patients with VLUs treated with SIS, HSE, or an advanced sterile wound matrix (Talymed® Marine Polymer Technologies, Inc, Danvers, MA) compared to standard care (compression therapy). Costs of treatment then were considered to determine the cost of an additional successfully treated patient. NNT point estimates of clinical efficacy were 2 for the advanced sterile wound matrix (95% CI; 2-8), 5 for SIS (CI; 3-39), and 6 for HSE (95% CI; 3-24). Incremental costs per additional successfully treated patient were \$1600 for the advanced sterile wound matrix, \$3150 for SIS, and \$29 952 for HSE. On this basis, SIS dressings appear to offer a more cost-effective solution than other advanced biologic dressings.

Carter et al[37] developed a Markov model to estimate the cost effectiveness of 3 topically applied CTPs used as adjunct therapies to best supportive care in the management of VLUs. CTPs evaluated in the study included SIS dressings, HSE, and LSE over the course of 1 year. The outcomes of interest were the number of ulcer-free weeks and expected costs of therapies

Table 1. Summary of small intestine submucosa (SIS) wound matrix dressing studies

Study	Population, sample size, and comparators Study design and duration	Outcomes and results
Randomized controlled trials (RCTs) in chronic wounds		
Mostow et al 2005[16]	**Population** Chronic full-thickness VLUs 120 patients ≥18 years **Intervention** SIS wound matrix plus standard care (n=62) Mean age 63±2 years Mean ulcer size 10.2cm^2 **Comparator** SC (ie, 4-layer compression bandaging) (n=58) Mean age 65±2 years Mean ulcer size 12.1cm^2 **Study design** Multicenter, prospective 12-week duration with weekly wound assessments 6-month follow-up for recurrence	**Healing rates at 12 weeks** 55% in the SIS wound matrix group 34% in the control group (*P*=.0196) Risk ratio (RR): 95% confidence interval (CI); 1.59 (1.04–2.42) **Mean dressing change frequency** SIS wound matrix: 1.8/week SC: 3.4/week **Time to healing** Probability of healing at 12 weeks: SIS wound matrix group=63% SC group=40% (*P*=.0226) **6-months follow-up recurrence** SIS=0 Comparator group=30% **Adverse events** No statistical differences in adverse events although the incidence was higher in control group; Total complications: 8 in the SIS group and 15 in the SC group, including more wound infections and hospitalizations in the SC group
Romanelli et al 2010[17]	**Population** VLU or mixed arterial/VLU 50 patients **Intervention** SIS wound matrix plus (n=25) Mean ulcer size 23.5cm^2 **Comparator:** Moist gauze (n=25) Mean ulcer size 25.2cm^2 **Study design** Single-center, prospective (no description of randomization) 8-week duration with weekly wound assessments 6-month follow-up to assess wound closure	**Incidence of healing at 8 weeks** SIS wound matrix=80% Gauze= 65% (*P* <.05) RR: 95% CI; 1.23 (0.86-1.75) **Time to healing** SIS wound matrix=5.4 weeks Gauze=8.3 weeks (*P*=.02) **Time between dressing changes** SIS wound matrix=5.2 days Gauze=2.1 days (*P*<.05) No adverse events were reported either group
Landsman et al 2008[24]	**Population** Diabetes, neuropathy leg ulcers 26 patients **Intervention** SIS wound matrix plus moist wound therapy (n= 13) Mean age 62.17±12.17 years Mean wound size 1.85cm^2 (1.83cm^2) **Comparator:** LSE plus moist wound therapy (n=13) Mean age 63.4±9.84 years Mean wound size 1.88cm^2 (1.39cm^2) **Study design** Single-center, prospective (no description of randomization; however, it was centralized) pilot study 12-week study with weekly wound assessments for 8 weeks then biweekly until 12 weeks 2-month follow-up to assess wound closure	**Incidence of healing at 12 weeks** SIS wound matrix=76.9% LSE=84.6% (*P* value not reported) RR: 95% CI; 0.91 (0.62-1.33) **Average time to healing** SIS wound matrix=35.67±41.47 days LSE=40.9±32.32 days (*P*=.73) **Average number of dressings applied** SIS wound matrix=6.46±1.39 LSE=2.54±0.78 Number of applications was estimated to cost $807 for SIS wounds, compared to $3505 for LSE wounds

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from a payer's perspective. Results demonstrated SIS dressings were the most cost-effective CTP when used in the management of VLUs as an adjunct to standard care. When compared to best supportive care, the estimated incremental cost effectiveness ratio of SIS was $86/ulcer-free day.

Guest et al[38] estimated the cost effectiveness from a Medicare perspective of using trilayer porcine SIS as an adjunct to standard care compared with standard care alone in managing DFUs in the US using a 6-state Markov model utilizing 2016 prices. The model costs were calculated over a 12-month period;

Table 1. Summary of small intestine submucosa (SIS) wound matrix dressing studies *continued*

Study	Population, sample size, and comparators Study design and duration	Outcomes and results
Romanelli et al 2007[25]	**Population** VLU or mixed arterial/VLU 50 patients ≥18 years **Intervention** SIS wound matrix (n=27) Mean age 64±3 years Ulcer duration 8.3 weeks Mean ulcer size 6.3cm^2 **Comparator:** Hyaloskin™ (Apeldoorn, The Netherlands) (n=27) Mean age 62±8 years Ulcer duration 7.2 weeks Mean ulcer size 5.6cm^2 **Study design** Single-center, prospective (no description of randomization) 16-week duration with weekly wound assessments 6-month follow-up to assess wound closure	**Incidence of healing at 8 weeks** SIS wound matrix=82.6% Hyaluronic dressing=46.2% (*P* <.001) RR: 95% CI; 1.91 (1.16-3.14) Approximately 80% more patients in the SIS group healed at 16 weeks compared to those in the comparator group. **Comfort (mean Visual Analaog Scale [VAS] score: 0 excellent to 10 critical)** SIS wound matrix=2.5 Hyaluronic dressing=6.7 (*P* <.01) **Pain (mean VAS score 0 none to 10 severe)** SIS wound matrix=3.7 Hyaluronic dressing=6.2 (*P* <.05) **Time between dressing changes** SIS wound matrix=6.4±1.4 days Hyaluronic dressing=2.4±1.6 days (*P* <.05)
Niezgoda et al 2005[26]	**Population** Chronic, full-thickness DFU in 73 patients **Intervention** SIS wound matrix (n=37) Mean age 58±2.3 years Mean ulcer size 5cm^2±1.4 **Comparator:** Regranex◊ Gel (Smith & Nephew, Fort Worth, TX) n=36 Mean age 57±1.9 years Mean ulcer size 3.2cm^2±0.5 **Study design** Multicenter prospective 12-week duration with weekly wound assessments 6-month follow-up for recurrence	**Incidence of healing at 12 weeks** SIS wound matrix=49% Becaplermin=28% (*P*=.055) RR: 95% CI; 1.75 (0.94-3.26) Using a 5% noninferiority bound results showed treatment with SIS wound matrix to be statistically noninferior to treatment with becaplermin (*P*=.0097) **Recurrence of ulcers at 6 months** SIS wound matrix =25% Becaplermin group= 3% (*P*>.05) **Time to healing** An improved trend in favor of SIS wound matrix at 7, 9, and 12 weeks but no difference between interventions was noted **Adverse events** No significant difference but slightly more infections in the SIS group 9 compared to 3 in the becaplermin group **Subgroup analyses 1:** Healing of ulcers located on plantar surface of the foot: SIS wound matrix=52% Becaplermin group=14% (*P*=.014) **Subgroup analyses 2:** Healing of ulcers in persons with type 2 diabetes SIS wound matrix=63% Becaplermin=29% (*P*=.034)

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clinical data were obtained from a published RCT by Cazzell et al.[27] The model results showed patients treated with SIS in addition to standard care had better clinical outcomes — specifically, it was estimated that patients treated with SIS had a 42% increase in the number of ulcer-free months, a 32% increase in the probability of healing, a 3% decrease in the probability of developing complicated ulcers, and a 1% decrease in the probability of undergoing an amputation compared to those treated with standard care alone. The total health care cost per patient of using SIS over 12 months was estimated to be $13 858 compared to $13 962 standard care alone, saving the health system $105 per patient. These findings were consistent in a sensitivity analysis where cost and clinical inputs were varied.

Gilligan et al[39] developed a 2-state Markov model based on a published RCT to estimate the cost effectiveness for SIS dressings relative to human fibroblast-derived dermal substitute (HFDS) on wound closure for the treatment of DFUs. A 12-week time horizon of weekly cycle length was employed. Clinical outcomes did not differ between the interventions. HFDS incurred substantially higher cumulative costs per DFU ($3889, £2524) compared to SIS dressings ($2522, £1634) (see Table 1). The authors concluded health

Table 1. Summary of small intestine submucosa (SIS) wound matrix dressing studies *continued*

Study	Population, sample size, and comparators Study design and duration	Outcomes and results
Cazzell et al 2015[27]	**Population** 82 patients with diabetes type 1 or type 2 ≥18 years **Intervention** SIS Ultra Tri-Layer Matrix (UBM; Smith & Nephew, Hull, UK) (n=41) Mean age 57.1±10.9 years **Comparator:** SC as selected by the study investigator, including silver dressings, hydrogel, wet-to-dry wound dressings, and triple antibiotic dressings (n=41) Mean age 56.6±10.8 years **Study design** Multicenter prospective open-label 12-week duration with additional 4 weeks' follow-up to assess wound closure	**Percentage of wounds closed** (defined as 100% reepithelialization, no drainage, and no need for a dressing) SIS UBM=54% (22/41) SC arm=32% (13/41) (*P*<.021) **Time to wound closure (weeks)** SIS UBM arm=9 (1.0 to 12.0) Standard care arm=11 (1.0 to 12.0) Probability of closure at 12 weeks: 62% versus 40% (*P*=.027) **Adverse events** No difference between SIS UBM and standard care
Observational prospective and retrospective studies in chronic wounds		
Barendse-Hofman et al 2007[28]	**Population** Patients (N=15) requiring skin grafting but not eligible due to high risk of postsurgical complications and excessive skin loss, making it impossible to use skin grafting or wound colonization requiring pre-procedure antibiotics Mean age 54.7 (range 19–85) years Mean wound duration 1.9 (range 1–4) months **Intervention** SIS wound matrix: 15 wounds without clinical signs of infection **Study design** Retrospective case note review	**Incidence of healing** Wound closure was achieved in 14 of the 15 patients (93.3%) **Time to healing** Mean: 1.6 months (range 0.5–5 months), 87% healed within 3 weeks **Adverse events** Complications included hypergranulation tissue formation (n=5) and infection (n=3)
Martinson and Martinson 2016[29]	**Population** DFU patients 13 193 skin substitute treatment episodes from the Centers for Medicare and Medicaid Services Standard Analytical Files 37.4% females 34% <65 years **Intervention and comparators (standard care plus)** HSE=4926 (37.3%) LSE=5530 (41.9%) SIS=2458 (18.6%) UBM=279 (2.1%) **Study design** Retrospective Medicare claims study (2011 to 2014) examining episode of care length, amputation rate, skin substitute utilization, and skin substitute costs	**Percentage healed at 90 days** UBM=62% SIS=63% HSE=58%; LSE=58% **Mean number of applications** UBM=5.5±7.9 LSE=6.0±4.6 HSE=3.2±2.8 SIS=4.5±4.0 **Total number of units of skin substitute (cm^2)** UBM=196±494 units HSE=190±289 units LSE=447±516 units SIS=155±334 **Mean costs per episode** UBM=$1435±$3160 HSE=$5364±$696 LSE=$14 424±$15 074 SIS=$1901±$5394 SIS and UBM costs significantly lower than HSE and LSE

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care providers should consider SIS dressings as a cost-saving alternative to HFDS.

SIS dressings in burns: clinical and patient outcomes. A single-center observational study by Cuenca-Pardo,[21] a prospective study,[22] and a case series[23] reported the clinical outcomes of treatment with SIS dressings, with facilitating reepithelialization as the key outcome measure. In the study by Cuenca-Pardo and Peralta-Conde,[21] wounds of 14 patients

Table 1. Summary of small intestine submucosa (SIS) wound matrix dressing studies *continued*

Study	Population, sample size, and comparators Study design and duration	Outcomes and results
Rando 2009[30]	**Population** Chronic wounds resulting from vascular impairment and other comorbidities, including Huntington's Disease, type 1 diabetes mellitus, chronic obstructive pulmonary disease, gout, and previous infections (N=4) **Intervention** SIS **Study design** Case series reports	**Healing rate** 50% after 12 weeks **Wound area** In 2 wounds that did not heal by week 12, decrease in area was 88.5% and 32.9% **Quality of life** Significantly improved quality of life as commented by the patients who said among other things "they were looking forward to getting on with living"
Carson et al 2003[31]	**Population** Patients (N=36) with chronic wounds that failed to heal using other treatment techniques **Intervention and comparator** SIS or becaplermin gel, collagen-alginate dressings **Study design** Observational study	**Complete healing rates** 67% in both SIS and collagen-alginate dressings 5 patients in each group healed enough to be closed with subsequent skin grafting **Healing time** 60 and 50 days, respectively, in SIS and collagen-alginate dressings groups
Brown-Etris and Hiles 2002[32]	**Population** Patients (N=15) with pressure, venous, trauma, or drug-induced wounds on the foot or lower leg **Interventions** Alternative formulation of hydrated SIS was compared to lyophilized SIS **Study design** Single-center pilot study comparing 2 different types of SIS wound dressing	**Incidence of healing at 8 weeks** Lyophilized SIS=100% Hydrated SIS=43% **Adverse events** No evidence of dressing-induced toxicity or clinical signs of rejection
Hampton 2002[3]	**Population** Patients with nonhealing chronic wounds (N=6) **Intervention** SIS **Study design** Case series	**Healing rates** 100% healing rates; no specified time to healing **Adverse events** No adverse events or clinical problems were noted
Olivares-Escutia et al 2002[34]	**Population** Chronic ulcers of any etiology (N=20) **Intervention** SIS Mean age 36.3 (range 13 to 82) years **Study design** Case series reports	**Healing rates** 90% of patients achieved healing (time to healing was not stated but is likely to be 12 weeks as one patient had 14 of the once weekly applications) **Number of applications required** Range 1–14 pieces
Lown et al 2005[35]	**Population** Patients with VLU (N= 33) **Study duration**: 12 weeks Mean age 66 years (range 38–75 years) **Intervention** SIS plus Unna boot compression (n=18) **Comparator** Unna boot only (n=15) **Study design** Retrospective chart review of patients treated with the 2 interventions	**Healing rates at 12 weeks** SIS=77% Unna boot=74% (P >.05) **Wound area reduction (cm^2)** No difference SIS=2.78±0.32 Unna boot=2.34±0.21 (P >.05)

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undergoing tangential excisions for facial burns were covered with SIS. Mean days to complete epithelialization in both second-degree and superficial burns was 8.8 ± 2.4 (range 7–14) days. The rate of epithelialization was 20% to 40% by the third week, and small lesions healed without grafts (see Table 1).

A prospective study by Salgado et al[22] of 5 patients with mid-thickness to partial-thickness burns reported that,

Table 1. Summary of small intestine submucosa (SIS) wound matrix dressing studies *continued*

Study	Population, sample size, and comparators Study design and duration	Outcomes and results
Studies in burn patients		
Cuenca-Pardo and Peralta-Conde 2011[21]	**Population** 14 patients with facial burns undergoing tangential excision **Intervention** SIS wound matrix plus moist wound therapy once bleeding was controlled Mean age 29.9±14.2 (range 2–65) years **Study design** Prospective, single-center observational study	Mean days to epithelialization=11.7±4.2 (range 7 to 21) days Second-degree and superficial burns: 100% epithelialization Mean days=8.8±2.4 (range 7–14 days) No evidence of scarring after removal of crust Third-degree burns: 20% to 40% epithelialization week 3, small lesions healed without grafts skin Grafting performed immediately upon removal of matrix Discomfort decreased and disappeared within 48 hours No complications reported (infection or deepening of the lesions)
Salgado 2014[22]	**Population** 5 patients with mid- to partial-thickness burns ≤10% of body surface **Intervention** SIS and AgH dressings and sterile gauze as the secondary dressing **Study design** Prospective, descriptive, patients served as their own control	**Mean epithelial maturation index** SIS=6.2±0.84 AgH=3.2±3.28 (*P*=.029) **Transforming growth factor–β3 expression** SIS=7.4±8.1 AgH=2.1±2.6 (*P*=.055) **Vancouver Scar Scale score** (3 months post treatment) SIS=3.6±2.6 AgH=7.2±2.5 (*P*=.025) Authors concluded that biological matrices favor the wound healing process
Cinat 2007[23]	2 patients with partial-thickness burns that had not healed with 14 and 33 days of SC (AgH), Alevyn◊ (Smith & Nephew, Hull, UK),, Hypafix™ (BSN Medical), Coban™ (3M, Loughborough, UK), and a hydrogel **Intervention** SIS	Case 1: 42-year-old man. Healed after 10 days. Excellent functional and cosmetic outcome at 4.5 months Case 2: 46-year-old man with scald burn who declined surgery/skin grafting on day 13. Wound was completely closed at 7.5 weeks. Very good functional and cosmetic outcome at 7 months
Health economics studies		
Hankin et al 2012[36]	**Population:** Patients with VLUs **Interventions:** SIS, HSEf, and advanced sterile dressing as adjuncts to compression therapy **Study design:** Economic analysis using data obtained from a review of published articles (from the earliest available Medline publication date to June 2011) from US payer's perspective	**Incremental costs (95% CIs) per additional successfully treated patient** SIS=$3150 ($1890–$24 570) Advanced sterile dressing=$1600 ($1600–$6400) HSE=$29 952 ($14 976-$119 808) **VLU episode of care costs** SIS=$630 Advanced sterile dressing=$800 HSE=$4992
Carter et al 2014[37]	**Population:** Patients with VLUs **Interventions:** ECM, SIS, HSE, LSE, and SC **Design:** a t3-state Markov model evaluated over 1 year from the payer's perspective	**Expected costs and outcomes** Standard care=$6132 and 24 ulcer-free weeks ECM (eg, SIS)=$6732 and 31 ulcer-free weeks HSE=$10 638 and 29 ulcer-free weeks LSE=$11 237 and 27 ulcer-free weeks ECM dominated other active comparators and is cost effective when compared with SC — ie, $86/ulcer-free day

Continued

compared to patients treated with a silver cellulose hydrofiber dressing (AgH; Aquacel® Ag; ConvaTec, Reading, Berkshire, UK) covered with sterile gauze, patients treated with SIS dressings had a higher epithelial maturation index (ie, progress of the epithelialization process and ranges between -2 and 8) (6.2 ± 0.84 versus 3.2 ± 3.28; P = .029). The study

Table 1. Summary of small intestine submucosa (SIS) wound matrix dressing studies *continued*

Study	Population, sample size, and comparators Study design and duration	Outcomes and results
Guest et al 2017[38]	**Population:** DFU patients **Interventions** SIS trilayer matrix SC that could include any of the following: silver dressing, hydrogel, wet-to-dry dressing, alginate dressing, Manuka honey, and triple antibiotic dressing **Design:** 6-state Markov model over a 12-month period using monthly cycle length from the third payer's perspective	At 12 months, use of adjunctive SIS compared to control led to a: • 42% increase in number of ulcer-free months • 32% increase in probability of healing • 3% decrease in probability of developing complicated ulcers • 1% decrease in probability of undergoing an amputation **Estimated total health care cost** SIS=$13 962 SC=$13 858 Sensitivity analyses showed that total cost of care for SIS remained lower compared to SC
Gilligan et al 2015[39]	**Population:** DFU patients **Interventions** ECM, SIS, HFDS **Design**: 2-state Markov model over a 12-week period using weekly cycle length from the third payer's perspective	**Cost per DFU** SIS=$2522 (£1634) HFDS=$3889 (£2524) (NS - *P*=.73) Sensitivity analyses showed total cost of care for 2 applications of HFDS was higher than 8 applications of SIS=approximately $500 [£325])

HSE=human skin equivalent; LSE=living skin equivalent; SC=standard care VLU=venous leg ulcers; DFU=diabetic leg ulcers; CPT=cellular/tissue-derived products; SIS=small intestine submucosa; AgH: silver hydrofiber dressing; ECM=extracellular matrix; NNT=number needed to treat; UBM=urinary bladder matrix; HFDS=human fibroblast-derived dermal substitute

also reported that patients treated with SIS dressings had better orientation and differentiation of epithelial cells, as well as an appropriate basal lamina structure, collagen deposition, and higher transforming growth factor–β3 expression (7.4 ± 8.1 versus 2.1 ± 2.6; $P = .055$) than tissues treated with AgH dressings. Furthermore, SIS dressings were not integrated in healed tissues, and after 3 months of treatment significantly ($P = .025$) less scarring was noted than with AgH dressing.

Finally, Cinat[23] reported on 2 cases of partial-thickness burns that had not healed after 14 and 33 days of standard care (Adaptic Touch™; Acelity, San Antonio, TX), Allevyn◊ (Smith & Nephew), Hypafix™ (BSN Medical, Hamburg, Germany), Coban™ (3M, St Paul, MN), and a hydrogel that then were treated with SIS dressings. The SIS-treated burns showed complete closure within 10 days for 1 case and 35 days with the other. Furthermore, closure was sustained at follow-up (4.5 and 7 months, respectively, for the 2 cases), with continued positive functional and cosmetic outcome, leading to avoidance of surgery.

Cost effectiveness in burns. No studies reported the cost effectiveness of SIS dressings in the management of burns, which reflects the low volume and quality of evidence on the use of these dressings in this indication.

Discussion

Wounds and burns, especially those that are persistent and complex, present a significant burden in all health care settings. Given the scale of this burden, the efficacy and cost-effectiveness of treatment approaches must be considered.

This review assembled the published clinical experience with porcine-derived SIS dressings in chronic wounds and burns evaluated using RCT and observational studies. Compared with other standard care modalities, the available evidence indicates SIS dressings offer enhanced clinical outcomes across multiple clinical goals, including complete wound closure, when compared with a number of alternative treatment options. Three (3) RCTs[16,17,25] reported statistically significant accelerated healing and wound closure in VLU wounds in favor of SIS compared to standard care and other active skin substitutes, 2 studies[26,27] found significant results in favor of SIS in DFU wounds, and 1 did not show any difference on healing outcome.[21]

The studies also report positive outcomes for SIS dressings on other patient outcomes. For example, data on patient-centered endpoints reported in key clinical SIS dressing studies compared with other skin substitutes demonstrate SIS dressings are less painful to remove, more comfortable to wear, easier to use, and easier to store.[21,26,36-38] Furthermore, cost modeling studies suggest the use of SIS as an adjunct to standard care was either cost saving (ie, resulted in fewer costs overall and better clinical outcomes) or cost effective when compared to standard of care alone in chronic wounds.[29,36-38] However, a need remains for further evidence on the value of SIS relative to standard dressings and other advanced treatment modalities that are used more widely in chronic wound care practice, such as negative pressure.

Although limited, evidence on SIS dressings used in the management of partial-thickness to full-thickness burns suggests these dressings may offer a safe, effective, and comfortable option for burn patients who may be candidates for grafting

but seek an alternative to surgery.[23] Initial observational studies[21,22] and case series[23] suggest SIS dressings have the potential to improve burn wound outcomes, but these study results should be considered exploratory and studies examining the dressing's efficacy and cost effectiveness are needed.

Limitations

This review was limited and not systematic, which may have biased the results. In addition, studies identified did not permit a meta-analysis to be conducted because they included different comparators including gauze, compression therapy, becaplermin wound gel, HSE, LSE, and hyaluronic acid biomaterial.

Conclusion

The results of this literature review show SIS dressings may improve outcomes in chronic wounds. Although evidence is limited, the dressings also show promise in burn management. In addition, the studies reviewed showed SIS dressing costs are lower than those of several alternative biological wound treatments. The current evidence suggests SIS dressings are safe and effective. Additional efficacy studies, especially in burn wound management, are warranted. ■

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