Supplemental Table 7. EVIDENCE ON ADJUNCTIVE THERAPIES

Modality	Evidence
Negative-pressure wound therapy	A systematic review of NPWT for chronic wound care in the home setting. Investigators could not draw conclusions about the efficacy or safety of NPWT for the treatment of chronic wounds in the home setting because of insufficient evidence. Consensus is needed on the methods of conducting and reporting wound care research so that future studies can inform clinical decisions.[1]
	Report on NPWT for infected wounds: no cost effectiveness recommendations given because of lack of evidence. "There remains a paucity of high-level evidence on [NPWT] in acute and chronically infected wounds of different origins. … Therefore, it is up to the practitioner to manage their patient's wound infection according to the best available evidence, which appears to be mostly of lower quality."[2]
	Recommendations on the optimal use of NPWT for the treatment of complex wounds from Quebec's Health Technology Agency: fairly detailed recommendations regarding initiation, discontinuation; document stresses interprofessional care approach and establishing a clear justification for starting NPWT.[3]
	Health technology assessment of DFUs and NPWT: NPWT appears to work better than other treatments for DFU postsurgery and does not appear to increase adverse events. Further, NPWT seems to be more cost-effective than other treatments for DFU, but this may vary by healthcare setting. Guidelines suggest that NPWT be considered for DFU in general, but recent Canadian guidelines cited a lack of evidence to support recommending its use.[4]
	Cochrane review of NPWT for surgical wounds healing by primary closure concludes: "…the evidence [was] judged to be of low or very low certainty for all outcomes. Consequently, uncertainty remains about whether NPWT compared with a standard dressing reduces or increases the incidence of important outcomes such as mortality, dehiscence, seroma, or if it increases costs. Given the cost and widespread use of NPWT for SSI prophylaxis, there is an urgent need for larger, well-designed and well-conducted trials to evaluate the effects of newer NPWT products designed for use on clean, closed surgical incisions." However, "People experiencing primary wound closure of their surgical wound and treated prophylactically with NPWT following surgery probably experience fewer SSI than people treated with standard dressings (moderate-certainty evidence)," and "decisions about use of NPWT should take into account surgical indication and setting and consider evidence for all outcomes."[5]
Electrical stimulation	Health technology assessment report on electrical stimulation for pressure injuries: "The committee concluded that there was too much uncertainty about the clinical benefit of adding electrical stimulation to high-quality standard wound care. This was largely due to a small body of evidence and to variation in how electrical stimulation and standard wound care were administered in the studies."[6]
Cellular and/or tissue-based products	• Review article on CTPs for chronic wound healing concludes: "The ideal skin substitute will inevitably only be found with the right direction, the right team, and the right amount of supporting clinical evidence."[7]
	• Systematic review conducted by US Veterans Affairs on advanced wound care therapies for nonhealing diabetic, venous and arterial ulcers including "biological skin equivalents" found mixed results depending on the modality and type of wound[8]
	• Systematic review of bioengineered CTPs for the management of wounds suggests products are more advantageous for DFUs than venous leg ulcer treatment, where little difference was observed between standard treatment and CTP use. Products with a dermal construct appeared to produce better wound healing than products with epidermal-only constructs.[9]
Skin grafting	• Systematic review and meta-analysis of the efficacy of EG for wound healing found autologous skin grafting is an important method for wound coverage; however, it is an invasive procedure and can cause donor site morbidity. Full-thickness skin graft is normally reserved for smaller wounds. The use of EG for wound healing has been on the rise of late; however, data on the outcomes and treatment groups have been heterogeneous. This systematic review found EG offers a healing rate of over 70% with mean healing time of 5 weeks and allows painless autologous skin growth.[10]
Ultrasound	• Systemic review focused on low-frequency ultrasound (20-60 kHz): although current studies are generally of smaller size, authors recommended the testing of low-frequency ultrasound therapy in clinical practice on a larger scale.[11]
	• Systematic review and meta-analysis of low-frequency (20-30 kHz) ultrasound delivered at either low or high intensity for wound healing: results showed early healing (at ≤5 months) in patients with venous stasis and diabetic foot ulcers was favorably influenced by both high- and low-intensity ultrasound delivered at a low frequency, either via contact or noncontact techniques. However, data quality may be suspect, especially for low-frequency low-intensity noncontact ultrasound because of significant biases. In patients presenting with either venous stasis or diabetic foot ulcers (Wagner classification 1-3), early healing appears to be facilitated by either low-frequency low intensity noncontact ultrasound or low-frequency high-intensity contact ultrasound.[12]

(continues)

Supplemental Table 7. EVIDENCE ON ADJUNCTIVE THERAPIES, CONTINUED

Modality	Evidence
Hyperbaric oxygen therapy	• Health technology assessment for HBOT for the treatment of DFUs: There is a large degree of uncertainty in both the clinical and economic evidence for HBOT, meaning that it is unclear how effective HBOT is and how cost-effective it is. Given this uncertainty, the authors decided the evidence was insufficient to make a recommendation to publicly fund or not fund HBOT for treating DFUs.[13]
	• Cochrane review of hyperbaric oxygen for DFUs concludes: "In people with foot ulcers due to diabetes, HBOT significantly improved the ulcers healed in the short term but not the long term and the trials had various flaws in design and/or reporting that means we are not confident in the results. More trials are needed to properly evaluate HBOT in people with chronic wounds; these trials must be adequately powered and designed to minimise [sic] all kinds of bias."[14]

Abbreviations: CTP, cellular and/or tissue-based product; DFU, diabetic foot ulcer; EG, epidermal grafting; HBOT, hyperbaric oxygen therapy; NPWT, negative-pressure wound therapy; SSI, surgical site infection.

References

1. Rhee SM, Valle MF, Wilson LM, Lazarus G, Zenilman JM, Robinson KA. Negative pressure wound therapy technologies for chronic wound care in the home setting: a systematic review. Wound Repair Regen 2015;23(4):506–17.
2. Negative Pressure Wound Therapy for Infected Wounds: A Review of Clinical Effectiveness, Cost-Effectiveness, and Recommendations for Use. Canadian Agency for Drugs and Technologies in Health: Ottawa, Ontario; 2015:1–26.
3. Toward the Optimal Use of Negative Pressure Wound Therapy for the Treatment of Complex Wounds. Institut national d'excellence en santé et en services sociaux: Quebec, Ontario; 2015:1–24.
4. Diabetic Foot Ulcers and Negative Pressure Wound Therapy: A Review. Canadian Agency for Drugs and Technologies in Health: Ottawa, Ontario; 2014:1.
5. Webster J, Liu Z, Norman G, et al. Negative pressure wound therapy for surgical wounds healing by primary closure. Cochrane Database Syst Rev 2019;3(3):CD009261.
6. Ontario Health Technology Advisory Committee. Electrical Stimulation for Pressure Injuries: OHTAC Recommendation. Health Quality Ontario: Toronto, Ontario; 2017:3.
7. Nicholas MN, Yeung J. Current status and future of skin substitutes for chronic wound healing. J Cutan Med Surg 2017;21(1):23–30.
8. Wrobel JS, Robbins JM, Charns MP, Bonacker KM, Reiber GE, Pogach L. Diabetes-related foot care at 10 Veterans Affairs medical centers: must do's associated with successful microsystems. Jt Comm J Qual Patient Saf 2006;32(4):206–13.
9. Barber C, Watt A, Pham C, et al. Bioengineered skin substitutes for the management of wounds: a systematic review. Database of Abstracts of Reviews of Effects: Quality-assessed Reviews. Centre for Reviews and Dissemination: York, United Kingdom; 2006.
10. Kanapathy M, Smith OJ, Hachach-Haram N, Bystrzonowski N, Mosahebi A, Richards T. Systematic review and meta-analysis of the efficacy of epidermal grafting for wound healing: systematic review on epidermal grafting. Int Wound J 2017;14(6):921–8.
11. Chang Y-JR, Perry J, Cross K. Low-frequency ultrasound debridement in chronic wound healing: a systematic review of current evidence. Plast Surg 2017;25(1):21–6.
12. Voigt J, Wendelken M, Driver V, Alvarez OM. Low-frequency ultrasound (20-40 kHz) as an adjunctive therapy for chronic wound healing: a systematic review of the literature and meta-analysis of eight randomized controlled trials. Int J Lower Extrem Wounds 2011;10(4):190–9.
13. Ontario Health Technology Advisory Committee. Hyperbaric Oxygen Therapy for the Treatment of Diabetic Foot Ulcers: OHTAC Recommendation. Health Quality Ontario: Toronto, Ontario; 2017:1–3.
14. Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE, Weibel S. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database Syst Rev 2015;2015(6):CD004123.