



# Supplementary Information: Adaptation of a Nature-Identical Material to the Needs of Advanced Chronic Wound Care

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**Table S1.** Clinical trials assessing different BC-based wound dressings in chronic wound care.

| Author                | Indication                                       | Study design                      | Patients  | Treatment  | Control   | Conclusion  |
|-----------------------|--|-----------------------------------|-----------|--|---|---|
| Alvarez et al. [1]    | Venous leg ulcers                                | Prospective RCT                   | 24 adults | Wet BC-dressing (XCell®) + compression                 | Nonadherent silicone dressing + compression     | More effective autolytic debridement; reduced time to granulation; greater wound area reduction; less wound pain                          |
| Portal et al. [2]     | Nonhealing lower extremity ulcerss               | Retrospective observational study | 11 adults | Dry BC-dressing (Dermafill™)                           | Various standard of care products               | Shortened time to wound closure over standard care  |
| Solway et al. [3]     | Diabetic foot ulcers                             | Prospective RCT                   | 30 adults | Dry BC-dressing (Dermafill™)                           | Petrolatum gauze                                | Faster wound closure rate   |
| Dini et al. [4]       | Venous leg ulcers                                | Prospective RCT                   | 46 adults | Wet BC-dressing (Suprasorb® X) + foam + compression    | Foam + compression                              | Improved leg ulcer healing and restoration of skin barrier function   |
| Cavalcanti et al. [5] | Venous leg ulcers                                | Prospective RCT                   | 25 adults | Wet non-commercial BC-dressing + gauze                 | Medium chain triglycerides oil + gauze          | Decreased pain; earlier discontinuation of analgesic use  |
| Colenci et al. [6]    | Venous leg ulcers                                | Prospective RCT                   | 46 adults | Dry BC-dressing (Nanoskin®) + compressive elastic band | Collagenase dressing + compressive elastic band | Similar results in both groups regarding pain, quality of life, safety; increased vascularization and promoted early wound healing for BC |
| Maia et al. [7]       | Lower limb revascularization of ischaemic wounds | Prospective RCT                   | 24 adults | BC-dressing + gel                                      | Essential fatty acids + gauze                   | Faster wound area reduction, higher complete healing rate after 90 days   |

**Table S2.** Clinical trials assessing different BC-based wound dressings in burn wound care.

| Author                  | Indication                     | Study design                          | Patients             | Treatment  | Control  | Conclusion   |
|-------------------------|--------------------------------|---------------------------------------|----------------------|--|--|--|
| Piatkowski et al. [8]   | Second-degree burns            | Prospective RCT                       | 60 adults            | Wet polyhexanide-loaded BC-dressing (Suprasorb® X)   | Silver sulphadiazine cream                           | Better and faster pain reduction, cost-effective and safe application of BC-dressing   |
| Aboelnaga et al. [9]    | Second-degree burns            | Prospective RCT                       | 40 adults            | Wet BC-dressing (EpiProtect®) + plastic film + elastic bandage                                 | Silver sulphadiazine cream + gauze + elastic bandage | Shorter hospitalization length, lower pain score during and after wound care, fewer dressing changes   |
| delli Santi et al. [10] | Second/third-degree burn       | Pilot study                           | 5 children           | Wet BC-dressing (EpiProtect®) after enzymatic debridement with Nexobrid™                       | -  | BC-dressing effective to heal pediatric burn wounds after enzymatic debridement  |
| Karlsson et al. [11]    | First-degree and excised burns | Retrospective comparative case review | 38 children & adults | Wet BC-dressing (EpiProtect®)  | Porcine xenograft                                    | Similar outcome for both groups, better pain relief for BC-dressing  |
| Cattalaens et al. [12]  | Second/third-degree burns      | Retrospective evaluation              | 56 children          | Wet BC-dressing (Epicite <sup>hydro</sup> ) + petrolatum gauze + dry compress                  | -  | Easy applicability, rapid re-epithelialization, excellent wound hydration, no wound-associated infections, no hypertrophic scars, good wound healing |
| Shanks et al. [13]      | First- to third-degree burns   | Prospective case series               | 30 children          | Wet BC-dressing (EpiProtect®) + silicone gauze   | -  | Effective analgesia for dressing changes, safe, reliable and well-tolerated for pediatric patients   |
| Maurer et al. [14]      | First- to third-degree burns   | Retrospective comparative trial       | 190 children         | Wet BC-dressing (Epicite <sup>hydro</sup> ) + non-adhesive gauze + dry compress                | Polyurethane foam dressing                           | Similar for wound healing, rate of complications and skin grafting, shorter hospitalization length and less interventions with anesthesia for BC     |
| Resch et al. [15]       | Second-degree burns            | Prospective case series               | 16 children          | Wet BC-dressing (Epicite <sup>hydro</sup> ) + non-adhesive gauze + dry compress                | -  | Undisturbed recovery of burn, frequency of dressing changes up to seven days   |
| Schiefer et al. [16]    | Second-degree burns            | Prospective open comparative trial    | 20 adults            | Wet BC-dressing (Epicite <sup>hydro</sup> ) + non-SUPRATHEL® skin substitute external dressing | -  | Similar outcome for both groups with regard to pain reduction, bleeding, infection, exudation, and scarring, better cost-effectivity for BC-dressing |

**Table S3.** Overview of wound diagnoses in BC\_A Post-Market Clinical Follow-up Study.

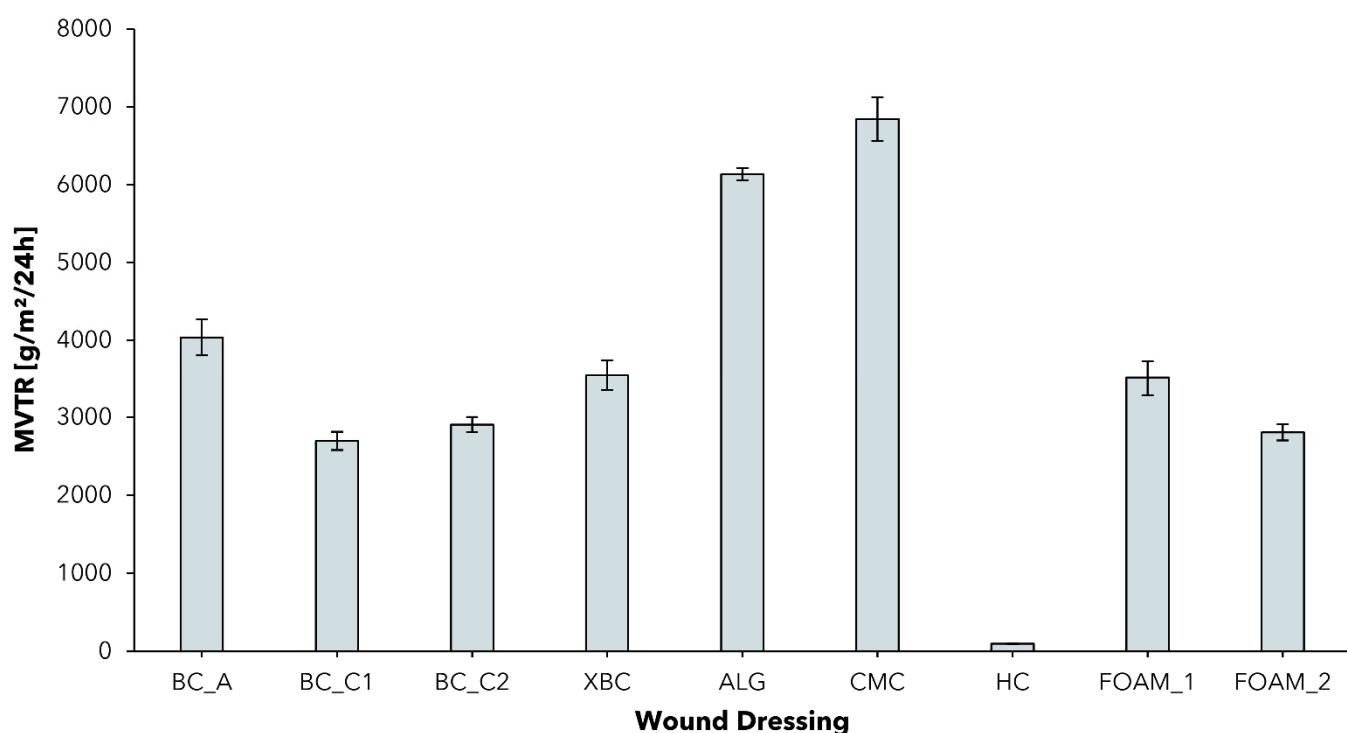
| Wound Diagnosis                   | Patient Count |
|-----------------------------------|---------------|
| Venous Leg Ulcer (VLU)            | 18            |
| Mixed Leg Ulcer (MLU)             | 8             |
| Diabetic Foot Syndrome (DFS)      | 4             |
| MLU + DFS                         | 1             |
| Wound Dehiscence                  | 1             |
| Decubitus Ulcer, unspecified      | 2             |
| Decubitus Ulcer Stage II          | 2             |
| Decubitus Ulcer, not assessable   | 1             |
| Charcot Foot, non-diabetic        | 1             |
| Leg Ulcer, concomitant vasculitis | 1             |
| Acne inversa                      | 1             |

**Table S4.** Overview of local wound treatment prior BC\_A Post-Market Clinical Follow-up Study.

| Previous Local Wound Treatment   | Patient Count |
|--|---------------|
| Sodium Carboxymethylcellulose (Hydrofiber) Dressing                            | 6             |
| Sterile Gauze  | 2             |
| Foam Dressing  | 3             |
| Alginate Dressing  | 2             |
| Hydrocolloid Dressing  | 1             |
| Polyester Contact Mesh with Medical Honey (Vivamel® Contact)                   | 2             |
| Silver-coated antimicrobial Dressing (Acticoat® Flex 3)                        | 1             |
| Antimicrobial hydrogel-impregnated Acetate Dressing<br>(Cutimed® Sorbact® Gel) | 1             |
| Silver-coated Alginate Dressing  | 3             |
| Iodine Solution  | 1             |
| Silver Sulphadiazine Cream (FLAMMAZINE®)                                       | 1             |
| Silver-coated Sodium Carboxymethylcellulose Dressing<br>(AQUACEL® AG)          | 4             |
| Silver-coated Absorbent Activated Charcoal Dressing                            | 4             |
| Absorbent Activated Charcoal Dressing  | 1             |
| ActiMaris® Wound Gel   | 1             |
| Medical Honey impregnated Gauze  | 2             |
| Hydrogel   | 2             |
| Hydrophobic Wound Dressing   | 2             |
| Various  | 1             |
| Unspecified  | 4             |

**Table S5.** Overview of causal therapy in BC\_A Post-Market Clinical Follow-up Study.

| Causal Therapy   | Patient Count |
|--|---------------|
| Compression Therapy                                      | 10            |
| Revascularization/ Percutaneous Transluminal Angioplasty | 2             |
| Abdominal Binder   | 1             |
| Regular Assessment of Ankle-Brachial Index               | 1             |
| Pressure Relief  | 6             |
| Supportive Orthosis                                      | 1             |
| Pharmacotherapy: Prednisolone                            | 1             |
| Pharmacotherapy: Metformin                               | 1             |
| Vacopaso® Free Therapy Shoe                              | 1             |

**Figure S1.** Moisture vapor transmission rate (MVTR) of different wound dressings determined with standard Paddington cup in contact with vapor method (mean  $\pm$  SD; n = 5).

## References

1. Alvarez, O.M.; Patel, M.; Booker, J.; Markowitz, L. Effectiveness of a Biocellulose Wound Dressing for the Treatment of Chronic Venous Leg Ulcers: Results of a Single Center Randomized Study Involving 24 Patients. *Wounds Compred. Clin. Res. Pract.* **2004**, *16*, 224–233.
2. Portal, O.; Clark, W.A.; Levinson, D.J. Microbial Cellulose Wound Dressing in the Treatment of Nonhealing Lower Extremity Ulcers. **2009**, *2*.
3. Solway, D.R.; Clark, W.A.; Levinson, D.J. A Parallel Open-Label Trial to Evaluate Microbial Cellulose Wound Dressing in the Treatment of Diabetic Foot Ulcers. *Int. Wound J.* **2011**, *8*, 69–73, doi:10.1111/j.1742-481X.2010.00750.x.
4. Dini, V.; Romanelli, M.; Andriessen, A.; Barbanera, S.; Bertone, M.S.; Brilli, C.; Abel, M. Improvement of Periulcer Skin Condition in Venous Leg Ulcer Patients: Prospective, Randomized, Controlled, Single-Blinded Clinical Trial Comparing a Biosynthetic Cellulose Dressing with a Foam Dressing. **2013**, *26*, 8.

5. Cavalcanti, L.M.; Pinto, F.C.M.; Oliveira, G.M.D.; Lima, S.V.C.; Aguiar, J.L.D.A.; Lins, E.M. Efficacy of Bacterial Cellulose Membrane for the Treatment of Lower Limbs Chronic Varicose Ulcers: A Randomized and Controlled Trial. *Rev. Colégio Bras. Cir.* **2017**, *44*, 72–80, doi:10.1590/0100-69912017001011.
6. Colenci, R.; Miot, H.A.; Marques, M.E.A.; Schmitt, J.V.; Basmaji, P.; Jacinto, J. dos S.; Abbade, L.P.F. Cellulose Biomembrane versus Collagenase Dressing for the Treatment of Chronic Venous Ulcers: A Randomized, Controlled Clinical Trial. *Eur. J. Dermatol.* **2019**, *29*, 387–395, doi:10.1684/ejd.2019.3608.
7. Maia, A.L.; Lins, E.M.; Aguiar, J.L.A.; Pinto, F.C.M.; Rocha, F.A.; Batista, L.L.; Fernandes, W.R. de M.A. Curativo Com Filme e Gel de Biopolímero de Celulose Bacteriana No Tratamento de Feridas Isquêmicas Após Revascularização de Membros Inferiores. *Rev. Colégio Bras. Cir.* **2019**, *46*, e20192260, doi:10.1590/0100-6991e-20192260.
8. Piatkowski, A.; Drummer, N.; Andriessen, A.; Ulrich, D.; Pallua, N. Randomized Controlled Single Center Study Comparing a Polyhexanide Containing Bio-Cellulose Dressing with Silver Sulfadiazine Cream in Partial-Thickness Dermal Burns. *Burns* **2011**, *37*, 800–804, doi:10.1016/j.burns.2011.01.027.
9. Aboelnaga, A.; Elmasry, M.; Adly, O.A.; Elbadawy, M.A.; Abbas, A.H.; Abdelrahman, I.; Salah, O.; Steinvall, I. Microbial Cellulose Dressing Compared with Silver Sulphadiazine for the Treatment of Partial Thickness Burns: A Prospective, Randomised, Clinical Trial. *Burns* **2018**, *44*, 1982–1988, doi:10.1016/j.burns.2018.06.007.
10. delli Santi, G.; Borgognone, A. The Use of Epiprotect®, an Advanced Wound Dressing, to Heal Paediatric Patients with Burns: A Pilot Study. *Burns Open* **2019**, *3*, 103–107, doi:10.1016/j.burnso.2019.05.001.
11. Karlsson, M.; Olofsson, P.; Steinvall, I.; Sjöberg, F.; Thorfinn, J.; Elmasry, M. Three Years' Experience of a Novel Biosynthetic Cellulose Dressing in Burns. *Adv. Wound Care* **2019**, *8*, 71–76, doi:10.1089/wound.2018.0790.
12. Cattelaens, J.; Turco, L.; Berclaz, L.M.; Huelsse, B.; Hitzl, W.; Vollkommer, T.; Bodenschatz, K.J. The Impact of a Nanocellulose-Based Wound Dressing in the Management of Thermal Injuries in Children: Results of a Retrospective Evaluation. *Life* **2020**, *10*, 212, doi:10.3390/life10090212.
13. Shanks, L.A.; Cronshaw, A.; Alexander, K.S.; Davies, J.A.; O'Boyle, C.P. Evaluation of EpiProtect® Microbial Cellulose Burns Dressings in Young Children. *Scars Burns Heal.* **2020**, *6*, 205951312094050, doi:10.1177/2059513120940503.
14. Maurer, K.; Renkert, M.; Duis, M.; Weiss, C.; Wessel, L.M.; Lange, B. Application of Bacterial Nanocellulose-Based Wound Dressings in the Management of Thermal Injuries: Experience in 92 Children. *Burns* **2021**, S0305417921001728, doi:10.1016/j.burns.2021.07.002.
15. Resch, A.; Staud, C.; Radtke, C. Nanocellulose-based Wound Dressing for Conservative Wound Management in Children with Second-degree Burns. *Int. Wound J.* **2021**, *18*, 478–486, doi:10.1111/iwj.13548.
16. Schiefer, J.L.; Aretz, G.F.; Fuchs, P.C.; Bagheri, M.; Funk, M.; Schulz, A.; Daniels, M. Comparison of Wound Healing and Patient Comfort in Partial-thickness Burn Wounds Treated with SUPRATHEL and Epicte <sup>hydro</sup> Wound Dressings. *Int. Wound J.* **2021**, iwj.13674, doi:10.1111/iwj.13674.