Topical Autologous Blood Clot Therapy: Consensus Panel Recommendations to Guide Use in the Treatment of Complex Wound Types

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ABSTRACT

The etiology of acute and chronic wounds goes beyond those often reported in the literature, including those with exposed structures, those in which the entire wound bed cannot be visualized, and patients who are not candidates for typical standard of care. Treatment options for these patients may be limited. TABCT is a viable option for these complex wound types and is not hindered by logistical, procedural, or patient factors. A consensus panel of providers with extensive experience in treatment of these wound types was convened to develop consensus recommendations on the use of TABCT in specific complex wound types. Four consensus statements were defined for TABCT use in patients who cannot undergo sharp or extensive debridement, as a protective barrier to prevent further bacterial ingress, in patients with wounds in which the entire wound bed cannot be safely visualized, and in wounds with exposed tendon and/or bone. Consensus panel recommendations show that TABCT application assists in maintenance of a moist wound healing environment, autolytic debridement, recruitment and delivery of factors essential for wound healing, prevention of pathogen entry, and ability to completely fill wound voids that cannot be fully visualized. Additional advantages of TABCT use are its cost-effectiveness, ease of access, minimal related complications, and proven clinical efficacy.

Keywords: debridement, extracellular matrix, fistula, tunneling, undermining

Many studies on wounds address only specific chronic wound types, such as DFU, VLU, and pressure ulcer (also referred to as pressure injury). This leads to an inadequacy in studies on acute and chronic wound types of other etiologies, including those with exposed tendon or bone, those with undermining and/or tunneling, fistulous wounds in patients with Crohn disease, wounds in patients who are not surgical candidates or who cannot undergo sharp debridement, arterial wounds in patients who have been maximally revascularized, and rheumatologic and hematologic ulcers. Such wounds are regularly defined as complex, or hard-to-heal wounds.[1,2]

Treatment with autologous blood therapy may be ideal for these patients given the readily available source and ease of access.[3,4] Autologous tissue therapy originating from blood may be a good option because it is autogenous, is easy to access, and has limited associated complications and procedural pain.[5]

Using TABCT, the provider can supply the patient's wound with the entire array of proteins, enzymes, cells, clotting factors, minerals, electrolytes, and dissolved gasses present within the blood that are essential to healing, leading to accelerated reduction in wound size and eventual resolution with full coverage of the wound.[6-12] TABCT is theorized to assist in wound healing by serving as a barrier to bacterial ingress; providing

Abbreviations: DFU, diabetic foot ulcer; DIME, debridement, infection/inflammation control, moisture maintenance, and wound edge preparation; EPUAP, European Pressure Ulcer Advisory Panel; NPUAP, National Pressure Ulcer Advisory Panel; TABCT, topical autologous blood clot therapy; VLU, venous leg ulcer.

Table. Wound Type Definitions

WOUND TYPE	DEFINITION
Acute	Soft tissue defect that has been present for <4 wk
Chronic	Soft tissue defect that has been present for ≥4 wk
Complex or hard to treat (ie, atypical)	An acute or chronic wound in which healing is complicated owing to several factors, including (but not limited to) the following: • Presence of exposed bone or tendon • Presence of undermining or tunneling or fistulous wounds • Wounds in compromised patients (eg, in patients with Crohn disease or rheumatoid arthritis) • Wounds in patients who are not surgical candidates • Arterial wounds in patients who have been maximally revascularized

Abbreviation: wk, week(s).

a temporary extracellular matrix, which serves as a signal and scaffold for cellular infiltration, migration, and interaction; modulating pain and inflammation; maintaining an optimal moist environment for healing; and assisting in autolytic debridement.[6-11] In addition, it has been shown that TABCT may increase oxygenated hemoglobin within the wound.[12] Little prospective evidence on the use of TABCT in wound management exists. There are no consensus recommendations for the best clinical practice.

International experts with extensive experience in wound care and surgical wound management were convened to develop expert- and evidence-based consensus statements to inform providers about the science behind TABCT use and how to incorporate TABCT in clinical practice. TABCT was introduced and the mechanisms of action explained in a previously published article.[13] The purpose of this article is to provide consensus recommendations on the clinical application of TABCT in complex, hard-to-heal wound types.

METHODS

Process of consensus panel recommendations

A core group of 9 clinicians from the United States and Germany with extensive experience in wound care and surgical wound management was convened with the objective of consensus development of decision pathways and recommendations for TABCT use in specific complex wound types. Specialties of the panelists included general surgery, vascular surgery, plastic surgery, podiatry, and infectious diseases. Literature on TABCT was provided for the panelists to review prior to the meeting to supplement their existing expertise and experience. Panelists were then assigned a specific topic and asked to present the current literature and their experience on the subject. These topics were as follows: definition of a complex wound, wound bed preparation, current autologous tissue therapies and their use in acute and chronic wound care, mechanisms of action of TABCT, and potential antimicrobial properties of TABCT. Specific wound types with which the clinicians had experience were discussed in detail, including the use of TABCT in wounds with exposed bone and tendon, atypical wounds, limb preservation, and treatment of perianal fistulas. Panelists then met in person to share introductions and these presentations, set objectives, and develop a consensus document for publication. Manuscript drafts were reviewed and revised per input from all panelists prior to agreement on the final document by all panel members.

CONSENSUS RESULTS

The initial publication resulting from the panel's efforts defined acute, chronic, and atypical wounds, that is, complex or hard-to-treat, wounds.[13] The agreed upon panel definitions from that publication are outlined in the **Table**. Implementation of TABCT use in the treatment of acute and chronic wounds was incorporated into use of the basic tenets of wound care common to all wound care guidelines, that is, addressing the underlying wound etiology and patient concerns, and performing wound bed preparation, including thorough debridement, infection/inflammation control, moisture maintenance, and wound edge preparation (DIME) (**Figure**).[14] Consensus statements were generated to inform providers how TABCT use fits into each category in the DIME model. It was difficult to compare TABCT use with outcomes following the use of other standard and innovative autologous treatment options owing to the lack or poor quality of published reports on TABCT use. This lack of guidance concerning effective treatment options for managing complex wounds served as the impetus for developing consensus statements for TABCT use.

Consensus statement 1

Topical autologous blood clot therapy should be applied to wounds after adequate debridement in patients in which this can be performed. Topical autologous blood clot therapy can also be used in patients who cannot undergo sharp debridement to create a moist wound healing environment conducive to autolytic debridement and delivery and recruitment of intrinsic factors essential for wound resolution.

Debridement is a key tenet in several wound care guidelines.[15-20] While the recommendation for debridement is strong, the quality of evidence to support debridement and the optimal modality for debridement remains sparse.[15] Guidelines on interventions to enhance healing of chronic DFUs, including debridement, found the 6 randomized controlled trials and 5 controlled cohort studies included

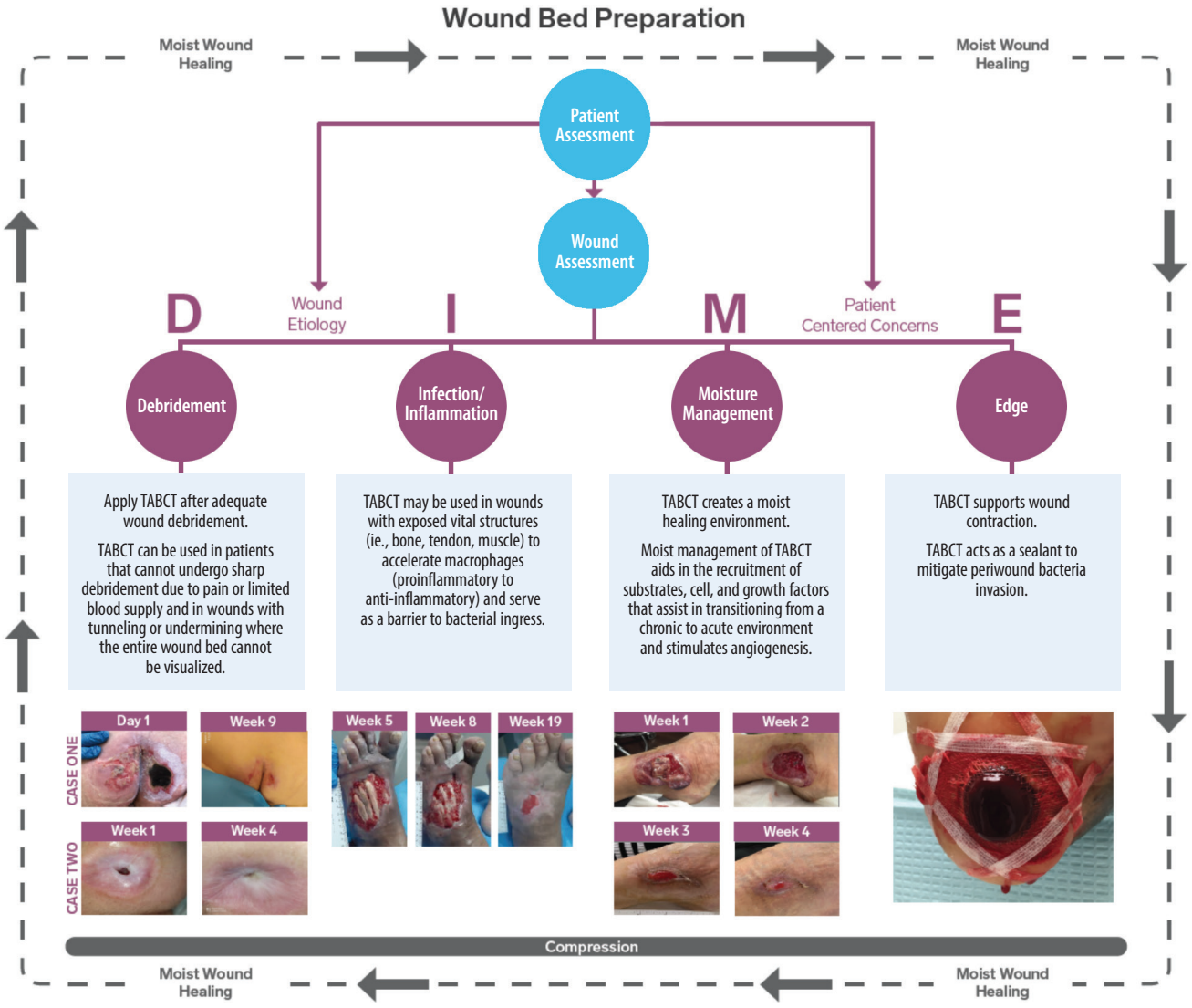

Figure. Incorporation of TABCT in acute and chronic wound care. Debridement, case 1: a 64-year-old-male with hypertension, hyperlipidemia, hypothyroidism, and iron and protein deficiency anemia with one month history of pressure injury on the buttocks. Resolution of pressure injury on left buttock at 1 week and 91% reduction in wound size of pressure injury to the right buttock in 9 weeks with 11 applications of TABCT, no adjunctive debridement performed. Previously published in Landau Z, et al. *Int Wound J*. 2022;10.1111/iwj.13927. Debridement, case 2: a 20-year-old male with quadriplegia and six-month history of tunneling ischial pressure injury. Past treatments included debridement and negative pressure wound therapy. Wound resolution was achieved in 4 weeks with 4 applications of TABCT. Infection/inflammation case: 65-year-old male with diabetes and severe neuropathy referred for amputation due to septic foot with exposed tendon and fascia. Wound achieved 91% reduction in wound size at 19 weeks with 12 applications of TABCT. Moisture management case: 37-year-old female with diabetes and iatrogenic vascular ulcer on the right lateral malleolus of two months, duration. Resolution achieved in 5 weeks with 4 applications of TABCT. Edge case: TABCT applied to a plantar heel ulcer in a patient with diabetes. Previously published in Snyder RJ, et al. *Wounds*. 2022;34(9):223-228. doi:10.25270/wnds/22011
Abbreviation: TABCT, topical autologous blood clot therapy.

to have a moderate to high risk of bias.[15] The overall conclusion was that debridement is likely beneficial in assisting with healing, with sharp debridement being the recommended modality of debridement.[15] However, several guidelines note limitations to the use of sharp debridement including severity of ischemia preventing extensive debridement, patient pain with debridement, patients with bleeding disorders or on anticoagulation therapy, and the capability and professional licensing restrictions of the health care provider.[15,16,18-20] Patients for whom revascularization is not an option reportedly have a 50% rate of limb loss and 25% mortality rate at 1 year.[21] In addition, if debridement is not an option owing to limited vascular supply, use of cellular and/or tissue-based products is often limited due to being contraindicated by the manufacturer's instructions for use and/or insurance company requirements for coverage. However, removal of infected and nonviable tissue

in these patients remains a core factor in progressing the wound toward resolution. Guidelines recommend autolytic debridement for these patients.[16-20] Autolytic debridement occurs when a moist wound environment is maintained. Debridement is achieved through components in the wound fluid that allow liquification of slough and the promotion of granulation tissue.[19] No articles were found that supported the use of other autologous tissue types to aid in debridement.

The consensus panel found that TABCT is a viable treatment option in this patient population given its ability to maintain a moist wound environment, ability to aid in autolytic debridement, cost-effectiveness, ease of access, minimal procedural and application-related complications, and efficacy in wound area reduction with use. Author J.C.L. found TABCT use in this patient population, in whom resection of gangrene was necessary, resulting in wounds with exposed tendon and bone, to be a low-cost autologous solution to serve as a biologic cover and achieve healing in some of these wounds (email communication, June 8, 2022). In an observational pilot study of 29 patients,[6] 21% of whom had mixed or arterial ulcers, 65% average percentage reduction in wound area was reported at 4 weeks; this increased to 94% at 12 weeks. One illustrative case involved an 80-year-old female patient with a mixed venous/arterial ulceration on the lower leg of greater than 12 months' duration. Use of red light and near-infrared light therapy and moderate compression bandaging did not progress the wound towards resolution. A 95% reduction in wound size was achieved with TABCT use. Another patient with a mixed venous/arterial ulceration was an 87-year-old male with a history of a lower extremity ulceration of 2 years' duration that had not progressed with other advanced wound care modalities. This patient healed at 17 weeks with the use of TABCT.[6]

Use of TABCT has also been reported to result in reduced pain in these patients in addition to achieving wound resolution, as noted in a case report of a 63-year-old male patient with a 1-year history of painful VLU of the left shin complicated by peripheral arterial disease and disability pain.[11] In that patient, serial weekly application of TABCT resulted in significant pain reduction at 5 weeks. The patient's pain level continued to improve, allowing return to activities of daily living and employment. Wound resolution was achieved at 15 weeks.

Consensus statement 2

Topical autologous blood clot therapy can be used to serve as a wound covering to prevent further bacterial invasion from commensal flora of the surrounding skin and the external environment.

One of the primary functions of human skin is to protect the body against bacterial invasion.[22] Symbiosis between the patient's cutaneous immune system and commensal flora helps prevent infection by opportunistic or other pathogenic bacteria.[22] In patients with diabetes, dysbiosis of the patient's cutaneous immune system and resident bacterial flora occurs, resulting in a greater diversity and selective overgrowth of antibiotic-resistant bacteria on the skin.[22-24] Increased sweat glucose concentrations, altered cutaneous thermoregulatory function, and reduced presence of Langerhans cells contribute to the constant subclinical inflammatory state, which makes the patient more prone to infection.[25-27] According to US Food and Drug Administration guidance, one stipulation for tissues designated as human/cellular tissue products according to section 361 of the Public Health Service Act and Title 21 of the Code of Federal Regulations Part 1271 is homologous use.[28] For human amniotic membranes, homologous use is defined as serving as a barrier to the external environment. This function should assist in prevention of infection. However, a systematic review and meta-analysis of randomized controlled trials on the use of human amniotic membrane in the treatment of DFUs reported minimal difference in infection rates compared with standard of care, with wound-related infection rates for wounds treated with human amniotic membrane ranging from 0% to 30%.[4]

The consensus panel noted that TABCT application may serve as a physical barrier to pathogens from the periwound skin and external environment. Application of TABCT to the wound bed provides a potential physical barrier to further bacterial ingress. This physical barrier has been shown to be effective for at least 12 to 27 hours following its application.[5] In addition to allowing time for the patient's own immune system to recruit the essential biological factors in the wound healing cascade, TABCT application also, theoretically, directly provides key essential antimicrobial factors to the wound and serves as a temporary scaffold and interaction interface for healing to occur via the mechanisms defined in previously published studies.[12,13]

Consensus statement 3

Topical autologous blood clot therapy is a viable treatment option for patients with fistulous wounds or wounds with undermining or tunneling in which the entire wound bed cannot be safely visualized or extensive debridement is not an option.

Fistulous tracts, tunneling, or undermining in wounds are common factors that can delay healing.[29-32] Visualization of the entire wound bed can be difficult or unobtainable, particularly in patients in whom tissue resection for full visualization is not possible.[33] Various types of advanced wound care products have been developed for use in these types of wounds, including surgical thread (ie, seton); negative pressure wound therapy; and powder or flaked formulations of xenograft, allograft, or placental products.[33,34] Reported time to healing in tunneling or undermining wounds treated with a flowable allograft or xenograft averaged 8 weeks.[35-37] Disadvantages of these products include potential inability to completely fill the void, painful and costly repeated dressing changes, product access and cost, and the potential for patient inflammatory

or immunogenic reactions to xenograft or allograft products.[33,34] No articles were found that supported the use of other autologous tissue types in fistulous wounds or wounds with undermining or tunneling.

The consensus panel found that TABCT use in these patients allows for more complete filling of these irregular areas within the wound, allowing for application of the entire consortium of beneficial factors in addition to the cost-effectiveness, ease of access, minimal procedural and application-related complications, and clinical efficacy associated with its use.

In a prospective, interventional pilot study of 7 patients with 9 NPUAP and EPUAP stage III or IV pressure injuries, use of TABCT resulted in complete healing in 7 of 9 (78%) wounds.[8] Healing was achieved with an average of 4 weekly applications (range, 1–7 applications). In the 2 patients who did not heal, an average reduction in wound size of 79.5% was achieved. The authors noted TABCT to be effective and safe in this patient population, most of whom were bedridden and all of whom had multiple comorbidities that adversely affect wound healing.

Consensus statement 4

Topical autologous blood clot therapy can be used in full-thickness wounds with exposed tendon and/or bone to serve as a barrier to bacterial ingress and assist in maintenance of a moist wound healing environment to aid in conversion from a proinflammatory to an anti-inflammatory state of healing and prevent desiccation and/or necrosis of exposed structures.

Wounds with exposed bone and tendon are at high risk for delayed healing and resultant amputation. These complications occur owing to the difficulty in obtaining recruitment of or formation of granulation tissue (ie, coverage) over these exposed structures. The longer these avascular structures remain exposed, the greater the risk for potential desiccation, necrosis, and secondary infections to occur.[39,40] High-quality literature on the use of advanced wound care modalities in these wounds has reported healing rates between 31.9% and 86.2%.[41-47] Use of a product that serves as a barrier to bacterial ingress and that maintains a moist wound to promote dynamic reciprocity in the wound bed and prevent desiccation and/or necrosis of exposed structures would be optimal in wounds with exposed bone and tendon.[48] Several studies included in a Cochrane review of autologous platelet-rich plasma in the management of chronic wounds specifically excluded wounds with exposed bone and tendon.[49]

The consensus panel found that TABCT fulfills all these requirements, in addition to its autologous nature and ease of access negating the need to wait for necessary supplies and time required to prepare autologous platelet-rich plasma, limited expense, and lack of contraindication for use or potential for patient reaction to the grafts.[50] As stated previously, this physical barrier created by application of TABCT to a wound has been shown to prevent bacterial ingress for the first 12 to 27 hours after application.[5] Moisture management of the wound is also maintained, which aids in autolytic debridement, prevention of desiccation and necrosis of exposed structures, and reestablishment of dynamic reciprocity to the wound bed by providing a temporary extracellular matrix scaffold and delivery and recruitment of cells, cytokines, and mediators, responsible for transition from a dysfunctional, inflammatory phase to the proliferative phase of wound healing.[48] As noted above, a pilot study[6] of TABCT use in hard-to-heal wounds, 55% of which had been present for over 12 months and greater than 75% of which had been treated with negative pressure wound therapy or split-thickness skin graft, reported an average reduction in wound size of 65% at 4 weeks and 94% at 12 weeks. One illustrative case from this pilot study included a patient with a DFU with exposed bone and a component of ischemia (Texas grade 3C) who had been scheduled to undergo amputation. TABCT was initiated in an attempt to prevent amputation. The patient achieved a 41% reduction in wound size at 4 weeks and a 97% reduction in wound size at 12 weeks. A patient with dehiscence following a transmetatarsal amputation achieved complete healing at 10 weeks following weekly TABCT application.

A case series reported on the results of 3 patients with complex wounds with exposed bone or tendon that was treated with TABCT.[48] The first patient had multiple comorbidities, including end-stage renal disease, peripheral vascular disease, and open transmetatarsal amputation performed for treatment of gangrene and extensive infection. After a single application of TABCT followed by 4 weeks of standard of care, the patient achieved complete coverage of all exposed structures. An 80% reduction in wound size was achieved by week 8. The second case involved a patient with multiple comorbidities, including rheumatoid arthritis, with a wound with exposed bone on the anterior shin. Complete wound resolution was achieved at 14 weeks following 4 applications of TABCT. The third patient had a pressure injury of the left heel with exposed bone complicated by osteomyelitis, severe peripheral vascular disease, and renal insufficiency. A below-knee amputation was recommended. The patient refused this treatment option because he had already undergone above-knee amputation on the contralateral limb. Eleven applications of TABCT resulted in wound resolution at 23 weeks.

DISCUSSION

The lack of studies on complex wound types, often seen daily in the inpatient and outpatient settings by experienced wound care providers, leads to a paucity of recommendations on optimal modalities to assist in wound resolution. Topical autologous blood clot therapy is a viable option in complex patients and complex wounds given the ready resource availability, ease of use, and capability to use the entire milieu of healing factors within the blood to assist with healing. Consensus panel recommendations have demonstrated the utility of TABCT to assist in autolytic debridement, protection from bacterial ingress, complete wound bed coverage, maintenance of a moist wound

healing environment, anti-inflammatory properties, and providing of nutrients and temporary structural support necessary for wound healing to occur.

LIMITATIONS

The primary limitation of these consensus recommendations is the lack of published studies on TABCT use in the management of complex wound types. While the amount of published literature on outcomes of TABCT in complex wounds is limited, new studies and multiple trials are currently underway to assess its impact on wound healing.[51-54] Previous publications on the science behind TABCT, review of available published reports, and the extensive experience of the panelists in wound care in general and TABCT in particular provide an evidence base supporting the benefits of TABCT use in complex wound care.[6-13]

CONCLUSION

TABCT offers several advantages over other autologous tissue types owing to the ability to include the entire milieu of healing components and factors that are found within whole blood and the creation of an environment that supports cellular activity and infection prevention. Consensus panel recommendations show TABCT application to be useful in the management of wounds owing to its inherent properties that allow it to maintain a moist wound healing environment; assist in autolytic debridement; recruit and deliver factors essential for conversion from a dysfunctional, inflammatory state to proliferation and wound healing; and prevent pathogen entry; and its ability to completely fill wound voids that cannot be fully visualized. These abilities in addition to the cost-effectiveness, ease of access, minimal procedural and application-related complications, and proven clinical efficacy of TABCT use make it a viable option in the management of wounds in patients who cannot undergo sharp debridement, who are at high risk for infection, and who have a wound with exposed bone and/or tendon, undermining, or tunneling.

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