The term complex wound is often used in the wound care literature, but defining this term is difficult. Although multiple studies cite contributing factors to and treatments for complex wounds, the complex or head-to-heal wound is difficult to define beyond one that does not follow the orderly and timely course of wound healing—that is, a chronic wound.1-7 Defining these wounds and optimizing management of them must move beyond the belief that chronicity is the only deciding factor in the definition of a complex or hard-to-heal wound. Acute and chronic wound types that can be complex or hard to heal include, but are not limited to, those with exposed tendon or bone,
undermining or tunneling ulcerations, fistulous wounds in patients with Crohn disease, venous leg ulcerations, wounds in patients who are nonsurgical candidates or who cannot undergo sharp debridement, arterial wounds in patients who have been maximally revascularized, and rheumatologic and hematologic ulcers. These wound types are often excluded in randomized controlled trials.

The common factor in the management of the above wound types is optimization of the patient and wound bed itself. Patient optimization involves assessing the physical, psychological, and social aspects that can hinder wound healing. Wound bed optimization involves removal of nonviable tissue and senescent cells, reduction of bacterial load, reduction of exudate while maintaining a moist environment, creation of a well-vascularized wound bed, and restoration of dynamic reciprocity to promote wound resolution.

Autologous therapies for complex wounds

Assessment of the entire patient rather than only the wound is necessary to improve outcomes. For example, the patient with a DFU is treated with appropriate offloading, management of hyperglycemia, maximization of perfusion, and assessment and management of the bacterial burden of the wound. In the patient with a venous stasis ulcer, treatment includes assessment of the venous anatomy and intervening, if necessary; application of adequate compression; and assessment and management of the bacterial burden of the wound. Holistic care can optimize treatment pathways for expeditious outcomes. Generally, management of these wounds should focus on patient- and provider-specific contributors to delayed healing, including patient age, comorbidities, pain, psychosocial factors, wound size and location, and microbial presence, as well as provider skill, knowledge, and access to available treatment options. Such a treatment approach can have a dramatic effect on the patient’s psyche in addition to increased expenditure for care.

In the appropriate patient and wound, autologous therapies may be ideal for wound closure. Examples include myocutaneous flap closure for a DFU, or split-thickness skin graft closure for venous stasis ulceration after optimal wound bed preparation. Use of autologous tissue negates the potential for patient rejection and accelerates healing compared with use of nonautologous products such as xenografts, allografts, and synthetic grafts. However, autologous flap and graft closure creates other possible morbidities, including a secondary donor site, increased pain, and potential delays in return to function. Other autologous tissue types, including tissue and cells derived from adipose, epidermis, dermis, bone marrow, and blood, have the same advantages as these more complex autologous tissue closure techniques without the associated disadvantages. Limitations of these other autologous tissue therapies include procedural pain, limited or contradictory evidence on their efficacy, the skill level required to perform the procedure, the potential need for an operating room, the creation of a secondary donor site, and the exclusion of patients who are not surgical candidates.

Of these autologous tissue types, those originating from blood may be the most sensible because it is an unlimited resource, easy to access, and has limited associated complications and procedural pain. A systematic review and meta-analysis of randomized controlled trials found that use of stem cells from peripheral blood resulted in similar outcomes on the healing of lower extremity ulcers compared with bone marrow aspirate (relative risk, 2.20 and 2.13, respectively). Rather than focusing on only a few specific blood cell types, such as platelets, endothelial progenitor cells, or granulocyte colony-stimulating factor–mobilized peripheral blood mononuclear cells, TABCT incorporates all of the essential factors present in blood and has been shown to reduce wound size, increase local tissue oxygenation saturation and angiogenesis, adjust local pH levels, and expedite wound healing (Figure 1). Also, TABCT has been shown to be cost-effective in chronic wound management compared with other commercially available advanced wound care products; it has the lowest cost.

Figure 1. Topical autologous blood clot therapy applied to a plantar heel ulcer in a patient with diabetes.

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per cm² with the highest healing efficacy at 12 weeks. This delay in bacterial ingress allows time for the patient's own immune system to recruit the essential cells of the inflammatory phase of healing to begin removal of damaged tissues and further prevent the potential for infection. One cell type that is critical in the inflammatory phase is the macrophage. Macrophages are unique in that they possess 2 phenotypes critical to the wound healing cascade. Within the deeper aspect of the blood clot, fibrin is organized in a more fibrous-like fashion. This configuration mimics the structure of the extracellular matrix, allowing for cellular infiltration, propagation, and interaction with the temporary scaffold structure of the clot to propagate the wound to the proliferative phase of healing.

In the proliferative phase, the M2 alternatively activated macrophage phenotype aids in granulation tissue formation and tissue repair. Transition between the M1 and M2 macrophage phenotypes is mediated by the macrophages themselves and the local wound environment. Topical autologous blood clot therapy delivers macrophages to the wound and provides the necessary environment to assist in wound resolution. The presence and interaction of the various components within blood results in fibroblast proliferation and angiogenesis, signifying the transition to the proliferative phase of healing. Interaction with the components in TABCT may also aid in wound bed preparation and modulation of inflammatory and pain signaling pathways, in addition to propagation to the proliferative phase of healing.

Fibrin is organized in a sheet-like fashion at the air-clot interface to prevent further clot growth. This physical barrier has been theorized to assist in healing by acting as a barrier to bacterial ingress; providing a temporary extracellular matrix that serves as a scaffold for cellular infiltration, migration, and interaction; modulating pain and inflammation; maintaining an optimal moist environment for healing; assisting in autolytic debridement; and increasing oxygenated hemoglobin within the wound.

Hemostasis, the first phase in the healing cascade, begins with activated platelets forming an initial platelet plug that contains red blood cells and fibrin. This clot matrix prevents further blood loss and serves as a barrier to bacterial invasion. Fibrin is organized in a sheet-like fashion at the air-clot interface to prevent further clot growth. This physical barrier has been shown to prevent bacterial ingress into the area of injury for the first 12 to 27 hours. This delay in bacterial ingress allows time for the patient's own immune system to recruit the essential cells of the inflammatory phase of healing to begin removal of damaged tissues and further prevent the potential for infection. One cell type that is critical in the inflammatory phase is the macrophage. Macrophages are unique in that they possess 2 phenotypes critical to the wound healing cascade. The M1 classically activated macrophage phenotype is responsible for host defense in the inflammatory phase of the wound healing

Science behind TABCT
The application of topical blood supports nutrient and waste exchange, regulation of pH levels, and infection prevention. Topical autologous blood clot therapy—which includes the entire array of proteins, enzymes, cells, clotting factors, minerals, electrolytes, and dissolved gases—is theorized to assist in healing by acting as a barrier to bacterial ingress; providing a temporary extracellular matrix that serves as a scaffold for cellular infiltration, migration, and interaction; modulating pain and inflammation; maintaining an optimal moist environment for healing; assisting in autolytic debridement; and increasing oxygenated hemoglobin within the wound.

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CONSENSUS PANEL DEVELOPMENT
A panel including clinicians from the United States and Germany with extensive experience in wound care and surgical wound management was convened on November 12, 2021, in Miami, Florida, 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 review by the panelists before the meeting to supplement their expertise and experience. Panelists were then assigned a specific topic to present current literature and their own experience on the subject. The assigned topics were 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. These included 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 the panelists prior to agreement on the final document by all panel members.

Future directions: decision pathways and recommendations for TABCT use
Although complex and hard-to-heal wounds can be acute or chronic and of various etiologies, commonalities exist in the complexity of care of these wounds. One commonality is the lack of well-defined treatment algorithms for most wound types, resulting in less than desirable outcomes with current therapies. Patient cofactors can contribute to these poor outcomes. Many clinicians agree that poor
Topical Autologous Blood Clot Therapy

Figure 2. The applications and advantages of TABCT exist on a continuum, able to adjust to the needs of the patient and the wound. 
Abbreviation: TABCT, topical autologous blood clot therapy.

Patient adherence with therapeutic plans is one such factor. Other factors include nonsurgical candidate status, inability to tolerate sharp debridement, and critical limb ischemia and tissue loss with no further vascular treatment intervention potential. Topical autologous blood clot therapy may be beneficial for these patients; it has the advantages of ease of access and availability of an unlimited resource with no need for a secondary donor site, it can be applied in a minimally invasive fashion without visualization of the entire wound bed or in a hostile wound environment (ie, perianal fistulas, pilonidal cysts), and it serves as a scaffold and barrier to bacterial ingress. These advantages make TABCT a practical autologous tissue therapy in patients with complex or hard-to-heal wounds (Figure 2). Patients with these conditions are often excluded in randomized controlled trials and in studies on the safety and efficacy of treatment modalities because of the high risk of failure. Subsequent articles will focus on consensus panel development of decision pathways and recommendations for TABCT use in the treatment of full-thickness wounds with exposed tendon and/or bone and undermining or tunneling wounds, wounds in patients who are nonsurgical candidates, those who cannot undergo sharp debridement, those with arterial wounds who have been maximally revascularized, and those with transsphincteric anal fistula.

Wounds with exposed structures, undermining, or tunneling
Ulcers with exposed tendon and/or bone are associated with a reduced likelihood of healing. These ulcerations are independent risk factors for infection and amputation. There is a paucity of high-quality literature on the use of advanced wound care modalities in these patients. The few studies on the use of advanced wound care modalities for these wound types, such as hyperbaric oxygen therapy, allografts, growth factor application, and negative pressure wound therapy, report healing rates between 56% and 88%. Additional procedures, such as split-thickness skin grafting, may also be necessary for complete resolution. Access to these advanced modalities may also be difficult and can be expensive for the patient and the health care facility. These ulcerations also are at increased risk of infection, which can lead to increased risk of morbidity and mortality owing to increased length of stay and the need for antibiotic therapy, surgery, or amputation. Topical autologous blood clot therapy may be beneficial in these settings because it can act as a barrier, providing coverage to help prevent further bacterial invasion, and assist with healing by providing coverage of these exposed structures that are prone to infection and desiccation. Because TABCT includes the entire consortium of blood elements, its antimicrobial ability may exceed that of autologous blood products that contain only some of the components of blood, such as PRP.

A case study on the use of TABCT to manage a DFU with exposed bone, tendon, and fascia demonstrated a reduction in wound size after 3 weeks of weekly TABCT application. Serial use of TABCT was credited with optimal wound bed management to allow healing to occur, including control of inflammation and infection, as well as optimal moisture management of the wound. A pilot study of TABCT for the treatment of hard-to-heal wounds also included patients with DFUs with exposed tendon and sinus tract formation. Serial application of TABCT resulted in a 97% reduction in wound size at 12 weeks. A case series of TABCT application in patients with complex wounds with exposed bone and tendon reported results ranging from 80% reduction in wound size and complete coverage of exposed structures with 100% granulation tissue at 8 weeks, to complete wound resolution at 23 weeks (range, 1–11 applications, respectively). A systematic review reported contradictory results on the potential antibacterial properties of PRP, noting that this treatment may be bactericidal or bacteriostatic based on the quantity and types of bacteria present in the wound, the patient’s immune status, and the dose of PRP given. Three clinical trials assessing the safety and efficacy of TABCT in the management of lower extremity wounds are currently underway. These studies include a prospective, postmarket survey; a multicenter observational study; and a multicenter, prospective, randomized, controlled,
single-blinded study. Outcomes of TABCT treatment on percent reduction of wound size, complete healing, and effect on pain will be assessed.

Fistulous, tunneling, or undermining in wounds also can contribute to delayed healing.\textsuperscript{6,64} Visualization of the entire wound bed can be difficult or unobtainable, particularly in patients in whom tissue resection for full visualization is not possible. Thus, no universally accepted standard treatment for tunneling and undermining wounds exists. Use of TABCT may be a viable option in these patients because it allows for application of the entire consortium of beneficial factors for healing as opposed to the use of 1 or a few autologous cell types. The flowable nature of TABCT helps ensure complete filling without the need for tissue resection to achieve full exposure. One proposed prospective, single-arm study will assess the utility of TABCT for complete wound closure, mean time to wound closure, percent wound area reduction, and durability of wound closure in adult female patients with postoperative dehiscence following laparotomy.\textsuperscript{65} The incidence of postoperative wound dehiscence following abdominopelvic surgery is approximately 3%.\textsuperscript{66} Ramifications of this postoperative complication can be extensive because of prolonged hospitalization and increased mortality.\textsuperscript{64} These wounds can be complicated by fistulas or tunneling or undermining within the wound bed. Recommendations about the optimal treatment of these wounds remain sparse. When conservative treatment is unsuccessful, the patient is often referred to plastic surgery for surgical closure. This treatment has been shown to require an average of 2 surgical procedures and almost 30 days for plastic surgery involvement and healing to occur.\textsuperscript{64} This same retrospective study found that time to healing was longest for wound dehiscence resulting from general surgical procedures. Hernia development, wound infection, wound redehiscence, and death were all potential complications of surgical management of these wounds. Use of TABCT may accelerate healing of these wounds and minimize the length of hospital stay and the potential for associated complications.

“No option” patient
Wound patients who are nonsurgical candidates, those who cannot undergo sharp debridement, and those with arterial wounds who have been maximally revascularized may be deemed “no option” patients. In such patients, tissue loss persists even though treatment has been optimized through medical management and vascular intervention. Published literature on this patient population is sparse, given the low potential for healing. The primary goal of wound care in such patients is management of pain, odor, bleeding, and exudate as well as infection prevention; healing is a secondary goal.\textsuperscript{67} In patients with advanced peripheral arterial disease, in whom vascular intervention has been maximized, healing rates range from 15% to 100%, and treatment often involves minor amputation.\textsuperscript{67} Optimal treatment would be low cost, with ease of access, availability, and application, as well as the potential for optimization of the wound bed for healing to occur or an option for palliative wound treatment. Serial application of TABCT in patients with ulcerations secondary to vascular insufficiency has reportedly resulted in wound area reduction of 95% and higher.\textsuperscript{7}

Transspincteric anal fistula
Optimal surgical management of transspincteric fistulas, similar to that of tunneling wounds, includes complete eradication of the opening without compromise of the anal sphincters.\textsuperscript{69,70} Surgical procedures can be divided into partial sphincter-preserving procedures (eg, fistulotomy, fistulectomy, cutting seton) and sphincter-conserving procedures (eg, ligation of the interspincteric fistula tract, drainage seton, mucosal advancement).\textsuperscript{70} Ligation of the interspincteric fistula tract has a long-term success rate of 37% to 84%.\textsuperscript{70,71} These rates are reportedly similar with the addition of a prosthetic graft or plug.\textsuperscript{72,74} Recurrence rates following any surgical intervention range from 2.5% to 57.1%, with a pooled recurrence rate of 19%.\textsuperscript{73} Factors associated with recurrence include previously recurrent fistula, presence of secondary tracks or branches as supraspincteric extension, high vs low transspincteric fistula, seton placement vs fistulotomy, multiple vs single tracts, anterior fistula, and horseshoe fistula.\textsuperscript{69,74} Female sex and horseshoe fistula were significant risk factors for recalcitrant incontinence after placement of a draining seton in patients with high transspincteric fistula in ano (P = .0002 and P = .01, respectively).\textsuperscript{67} A meta-analysis of autologous stem cell therapy for the treatment of anal fistula in patients with Crohn disease demonstrated higher efficacy rates and a lower incidence of adverse events compared with conventional therapies.\textsuperscript{75} Treatment with TABCT may be a viable option in these patients for the same reasons its use may be beneficial in the management of undermining or tunneling wounds.

LIMITATIONS
The primary limitations are the lack of published data on the use of TABCT in the management of complex wounds, the lack of knowledge of the extent of viability and amount of healing factors present in each aliquot of blood, and how this may vary from patient to patient. Although the published literature on the utility of TABCT in complex wound care is limited, future publication of multiple trials currently underway assessing its safety and efficacy, and the forthcoming publications on consensus recommendations on the use of TABCT in complex wound care, is expected to expand this evidence base. The science behind the multiple components of blood and their interaction referenced herein demonstrate the potential for TABCT to facilitate wound bed optimization. Future studies on quantification and assays of multiple TABCT patient samples would provide an improved understanding of inter-sample variability and how this may affect wound healing.
CONCLUSION
This article provides background knowledge on the science behind TABCT use and its potential for treatment of complex wounds. Use of TABCT offers several advantages over other autologous tissue types due to inclusion of the entire milieu of healing components within blood and the creation of an environment that supports cellular activity and infection prevention. Consensus panel development and recommendations on the use of TABCT in specific complex wound types will be provided in forthcoming publications in this series. Future publications will discuss the safety and efficacy of TABCT use in full-thickness wounds with exposed bone and/or tendon, undermining, or tunneling; in wounds in patients who are nonsurgical candidates or who cannot undergo sharp debridement; in arterial wounds in patients who have been maximally revascularized; and in patients with transsplan-}

terinal anastomosis.

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