Surgical Pathology to Describe the Clinical Margin of Debridement of Chronic Wounds Using a Wound Electronic Medical Record

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BACKGROUND: Chronic wounds, including diabetic foot ulcers (DFU), pressure ulcers (PU), and venous ulcers (VU) result from multiple physiologic impairments. Operative debridement is a mainstay of treatment to remove nonviable tissue and to stimulate wound healing. Unlike tumor resection, however, operative wound specimens are not routinely sent for pathology. The objective of this study was to describe the pathology present in chronic wounds.

STUDY DESIGN: Pathology reports of the skin edge and wound base from 397 initial debridements in 336 consecutive patients with chronic wounds were retrospectively reviewed. All data were entered and stored in a Wound Electronic Medical Record. Pathology data were extracted from the Wound Electronic Medical Record, coded, and quantified.

RESULTS: Up to 15 distinct histopathologic findings across 7 tissue types were observed after review of pathology reports from chronic wounds. Specifically, the pathology of epidermis revealed hyperkeratosis: 66% in DFUs, 31% in PUs, and 29% in VUs. Dermal pathology revealed fibrosis in 49% of DFUs, 30% of PUs, and 15% of VUs. Wound bed pathology revealed necrosis in the subcutaneous tissue in 67% of DFUs, 55% of PUs, and 19% of VUs. Fibrosis was reported in between 19% and 52% of all wound types. Acute osteomyelitis was present in 39% of DFUs, 33% of PUs, and 29% of VUs.

CONCLUSIONS: This observational study of the histopathology of initial surgical debridement of chronic wounds revealed a wide range of findings across multiple tissue levels. Although certain findings such as osteomyelitis and gangrene have been shown to directly relate to impaired wound healing and amputation, other findings require additional investigation. To rigorously define a margin of debridement, a prospective study relating histopathology and clinical outcomes such as healing rates and amputation is needed. (J Am Coll Surg 2009;209:254–260. © 2009 by the American College of Surgeons)

Chronic wounds such as pressure ulcers (PU) (eg, bed sores), diabetic foot ulcers (DFU), or venous ulcers (VU) are not defined by their duration but rather by their physiologic impairments to healing.[1] The morbidity and mortality associated with chronic wounds is staggering. In particular, up to 54% of stage IV PUs require multiple hospital admissions[2,3] and are often complicated by osteomyelitis.[4] The 6-month mortality rate of patients with stage IV ulcers has been reported to be as high as 68.9%.[5] Persons with diabetes have a lifetime risk of a foot ulcer developing that is as high as 25%.[6] The presence of an ulcer increases the risk of lower extremity amputation by almost six-fold.[7] The 5-year survival rate of major amputees with diabetes is approximately 31%.[8] Although VUs are less well studied than pressure and diabetic foot ulcers, they afflict from 0.06% to 2% of patients[9] and cost the health care system between $1.9 billion and $2.5 billion.[10]

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Abbreviations and Acronyms
DFU = diabetic foot ulcer
PU = pressure ulcer
VU = venous ulcer
WEMR = Wound Electronic Medical Record

Despite the morbidity and mortality that result from chronic wounds, little is known about their molecular and cellular abnormalities. Multiple causes such as decreased impaired innervation,[11] direct pressure,[12] inadequate angiogenesis,[13] microcirculatory ischemia[14] and impaired cellular migration,[15] venous reflux,[16] and abnormal keratinocyte activation and differentiation[17] all play a role. Experimental data suggest aberrant gene regulation at the edges of chronic wounds that may be responsible for impaired cellular migration.[15,18] Although there is emerging knowledge about molecular mechanisms behind impairment of healing in chronic ulcers, there have been few reports about how clinicians can identify these impaired cells and remove them.

Although sharp debridement is an accepted technique to remove impaired cells, has level 1 evidence in accelerating wound healing,[19,20] and is advocated in multiple consensus guidelines,[21-23] exactly where to debride—both how wide and how deep—the "negative margin" for chronic wounds has not been characterized. Before defining a margin of debridement, however, more knowledge of the type of pathology that resides within a chronic wound is needed. The rationale for healing of chronic wounds, ie, a wound bed with granulation tissue and free of necrosis, has been established for more than 50 years.[24] Although studying pathology from debrided PUs can provide a rational basis for surgical debridement, only animal models[25] and limited studies of human skin[26] are available.[27]

The objective of this study was to describe the pathology at various histologic levels from DFUs, PUs, and VUs.

METHODS

Patients were admitted for surgical debridement and treated at a university-based tertiary care hospital in a dedicated wound healing unit. All surgical specimens were obtained from the initial surgical debridement for a particular wound under sterile conditions. In some cases, as in the patients with PUs, more than one wound may have been debrided in the initial operation, and these results are reported. The operating surgeon identified tissue for pathology using the designation skin, subcutaneous tissue, fascia, tendon, muscle, or bone. Routine hematoxylin and eosin stains were used to evaluate all specimens.

All patient data were entered into a MS Access called the Wound Electronic Medical Record (WEMR), which was specifically designed to track unique wound-related variables. A coding system was developed to extract the narrative pathology reports from the WEMR into a quantifiable form. Each tissue level (eg, epidermis, dermis) had a specific alphanumeric code, as did the pathology report finding (eg, hyperkeratosis, fibrosis). Each specific finding was assigned a letter code in a spreadsheet. A tissue code was developed as the following: E, epidermis; D, dermis; S, subcutaneous tissue; F, fascia; T, tendon; M, muscle; and B, bone. A diagnosis code was similarly developed: K, hyperkeratosis; A, acanthosis; I, inflammation; G, gangrene; N, necrosis; F, fibrosis; GT, granulation tissue; AO, acute osteomyelitis; and T, atrophy.

After local Institutional Review Board approval, this methodology was used to review and code pathology reports from the initial operative debridements of 139 consecutive patients with VUs, 98 consecutive patients with DFUs, and 139 initial debridements from 98 patients with PUs.

Chronic wound biopsies of the skin edge, wound bed, and bone were obtained. All specimens were sent to the core pathology service for processing. A small portion of the specimens were fixed in formalin and processed for paraffin embedding. Paraffin embedded tissue was sectioned and 5-μm thick sections were stained with hematoxylin and eosin. The sections were analyzed using a Carl Zeiss microscope (Carl Zeiss).

RESULTS

Full results are reported in Tables 1 to 3, and values are the percentage of the pathologic finding reported per tissue level.

Wound edge: epidermis and dermis

The predominant findings in the epidermis were hyperkeratosis; 66% of all epidermal specimens in DFUs, 31% in PUs, and 29% in VUs had hyperkeratosis (Figure 1A shows the multiple layers of keratinocytes in the cornified layer of skin). Parakeratosis, the presence of nuclei in the cornified layer, was also noted in 29% of specimens from DFUs (Fig. 1B). Necrosis, as expected, was most prominent in DFUs (32%) and PUs (29%).

Histologic examination of the dermis is critical in evaluating whether the cells left behind after debridement will stimulate closure (granulation tissue) or will not, (eg, fibrosis). Although gangrene was reported in up to 12% of dermal specimens, the more clinically subtle finding of fibrosis was seen in 49% of DFUs, 30% of PUs, and 15% of VUs. At the opposite end of the spectrum, granulation tissue was seen in 64% of DFUs, 80% of PUs, and 60% of VUs.

Table 1. Percentage of Pathology Reports Containing Specific Histologic Findings in Venous Ulcers

	Tissue level, % of total reports						
Pathology finding	**Epidermis (n = 117)**	**Dermis (n = 109)**	**Subcutaneous (n = 21)**	**Fascia (n = 9)**	**Tendon (n = 4)**	**Muscle (n = 4)**	**Bone (n = 7)**
Hyperkeratosis	29						
Acanthosis	3						
Inflammation	85	89	71	44	50	25	43
Granulation tissue		80	48			25	6
Necrosis	13	14	24	33	25		29
Gangrene	3	2	0			0	
Fibrosis		15	19		25	25	0
Osteomyelitis							29
Viable tissue			14	11		25	14
Nonviable tissue			5			16	
Atrophy						50	

Wound bed: subcutaneous tissue

A similar histologic distinction was found in the subcutaneous tissue between viable and nonviable tissue as it was in the dermis. Soft tissue or fat necrosis was reported in more than half of all DFUs and PUs (67% and 55%), respectively. Fibrosis, characterized by acellular woven strands of collagen, was seen in all types of wounds. An example from a PU is shown in Figure 2A; contrast this tissue with granulation tissue (Fig. 2B), also from a PU wound bed.

In addition, tissue clinically identified as either fascia or tendon was sent to pathology for routine hematoxylin and eosin staining. Necrotic fascia was identified in 67% of DFUs and 33% of VUs. Fibrosis was reported in 80% of DFUs, 21% of PUs, and 33% of VUs. Tendon was not commonly identified.

Wound bed: muscle and bone

Examination of hematoxylin and eosin staining of muscle and bed is particularly of interest in debridement of stage III and stage IV PUs. Presence of fibrosis and infection indicates that additional surgical treatment is needed. Atrophic muscle was a relatively common finding, as indicated by the less robust myocyte with a decentralized nucleus.

Acute osteomyelitis, characterized by presence of bone surrounded by an inflammatory infiltrate of lymphocytes and neutrophils, was prevalent in both DFUs (39%) and PUs (33%) (Fig. 3A). Chronic osteomyelitis was reported in 18% of DFUs, 20% of PUs, and 29% of VUs (acute or chronic). Also of interest was fibrotic bone, as can be seen in Figure 3B, which shows areas of pink bone interrupted by areas of acellular light pink material. Bone that has be-

Table 2. Percentage of Pathology Reports Containing Specific Histologic Findings in Diabetic Foot Ulcers

	Tissue level, % of total reports						
Pathology finding	**Epidermis (n = 77)**	**Dermis (n = 78)**	**Subcutaneous tissue (n = 43)**	**Fascia (n = 10)**	**Tendon (n = 3)**	**Muscle (n = 5)**	**Bone (n = 28)**
Hyperkeratosis	66						
Parakeratosis	34						
Acanthosis	13						
Pseduoepithelimatous hyperplasia	25						
Granulation tissue		64	51	70			11
Gangrene	9	12	9	30			7
Inflammation			41	60	33		
Fibrosis		49	51	80	33		36
Necrosis	32	38	67	40	100	20	36
Acute osteomyelitis							39
Chronic osteomyelitis							18
Reactive bone							7
Abscess		21	28	20			
Viable tissue				10			11
Atrophy						80	
Normal	1						

Table 3. Percentage of Pathology Reports Containing Specific Histologic Findings in Pressure Ulcers

	Tissue level, % of total reports						
Pathology finding	**Epidermis (n = 107)**	**Dermis (n = 105)**	**Subcutaneous tissue (n = 87)**	**Fascia (n = 14)**	**Tendon (n = 7)**	**Muscle (n = 17)**	**Bone (n = 70)**
Hyperkeratosis	31						
Parakeratosis	9						
Acanthosis	6						
Granulation tissue		60	38	57		6	20
Inflammation	48	66	51	71	43	41	
Fibrosis		30	32	21		24	
Necrosis	29	24	55		43	12	14
Acute osteomyelitis							33
Chronic osteomyelitis							20
Reactive bone							21
Nonviable tissue			1				3
Viable tissue			2		14		4
Atrophy						29	
Gangrene	4	4	11	29	14	6	
Normal	6	7					

gun to heal is termed reactive bone; an example from a PU can be seen in Figure 3C and was identified in 21% of PUs and 7% of DFUs.

DISCUSSION

This study characterizes the pathology of 397 initial operative debridements of chronic wounds. Pathologists reported on up to 15 different histopathologic findings across 7 different tissue levels as the data reveal. Although there are not sufficient data to conclude that pathologically authoritative debridement heals wounds and faster, we have suggested a structure for multiple hypotheses that could be tested; for example, the width of debridement is characterized by absence of hyper- and parakeratosis at the skin edge, the depth of debridement is characterized by absence of fibrosis (ie, cellular infiltrate) and infection, or presence of granulation tissue in the dermis and deeper tissues is a reliable marker of a healing wound.

How wide to debride a wound?

The clinical margin of debridement has traditionally been to debride "to where it bleeds" or to where the surgeon thinks the skin appears "normal." In DFUs, debriding callus is well accepted and this technique using histopathologic margins has recently been described.[28] These data revealed that the primary abnormal finding in the skin edge of chronic wounds is hyperkeratosis. In an acute wound, hyperkeratosis is a normal response to wounding. But in a nonhealing wound, previous studies have suggested that hyperkeratosis represents abnormal keratinocyte activation and differentiation and that these cells may have an impaired ability to migrate.[15,17]

This study revealed predominance of granulation tissue in the dermis of chronic wounds. Granulation tissue was noticed in between 60% and 80% of all specimens; fibrosis was seen in between 15% and 49% of specimens. Histology shown in Figure 2 demonstrates the contrast between these two types of tissue, which may or may not be distinguished in the operating room, but are clearly very different on analysis.

These data suggest that the surgeon should debride a wound until there is an absence of hyperkeratosis in the epidermis and an absence of fibrosis in the dermis. But a caveat to this hypothesis occurs in VUs. Although the wound of a VU is defined by a break in the epidermis, the entire leg skin on a patient with a VU is typically abnormal and often fibrotic. Because removing all the fibrotic skin is neither practical nor safe, the skin edge is excised approximately 1 cm past the wound edge. These initial observations of the skin edge in chronic wounds require prospective study to evaluate whether or not their identification makes a difference in clinical outcomes.

How deep to debride a wound?

Presence of fibrosis and infection, particularly osteomyelitis in the wound bed, were abnormal findings in all three wound types and should be removed. Fibrosis (scar) was seen in up to 51% of specimens containing subcutaneous tissue and up to 36% containing bone. These acellular strands of collagen (Fig. 2A) should be removed to allow for development of well-vascularized granulation tissue (Fig.

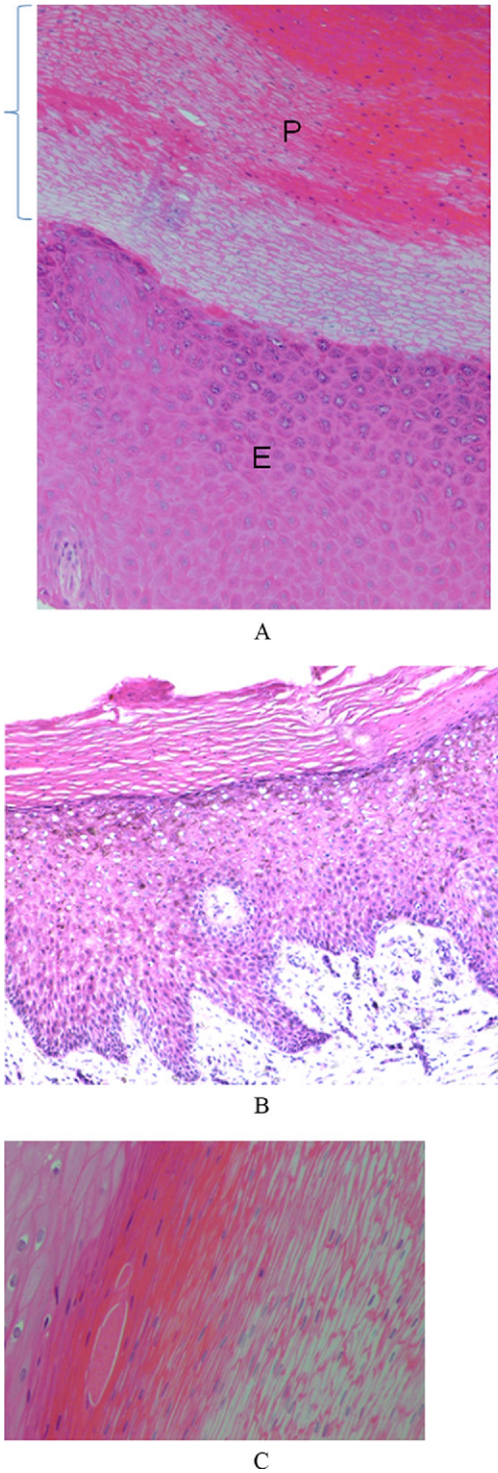


Figure 1. (A) Epidermis of the wound skin edge showing hyperproliferative epidermis, hyperkeratosis (thickened stratum corneum, indicated by the bracket) and parakeratosis, indicated by the presence of nuclei in the stratum corneum. (B) Low power of thickened epidermis and hyperkeratosis in a venous ulcer. (C) High power of parakeratosis; note purple nuclei. Prepared with routine hematoxylin and eosin staining. E, epidermis; P, parakeratosis.

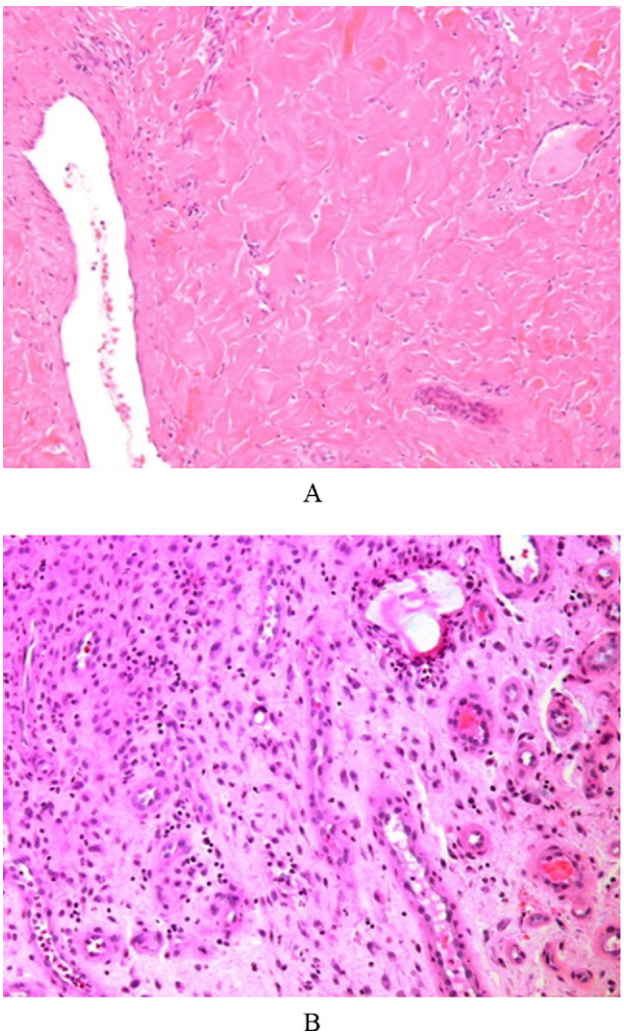
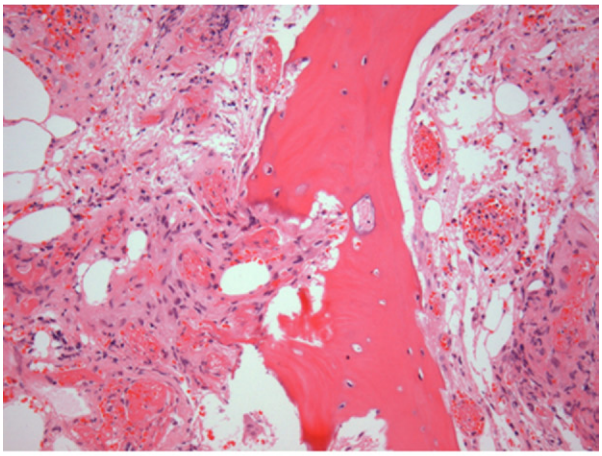


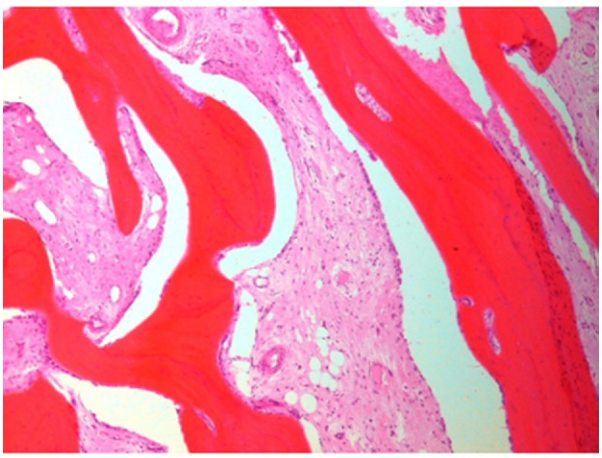
Figure 2. (A) Dermal fibrosis characterized by acellular strands of woven collagen. (B) Dermis with granulation tissue, characterized by multiple inflammatory cells and presence of multiple blood vessels. Prepared with routine hematoxylin and eosin staining.

2B). For most surgeons, it is nearly impossible to precisely determine how deep to debride based purely on gross inspection.

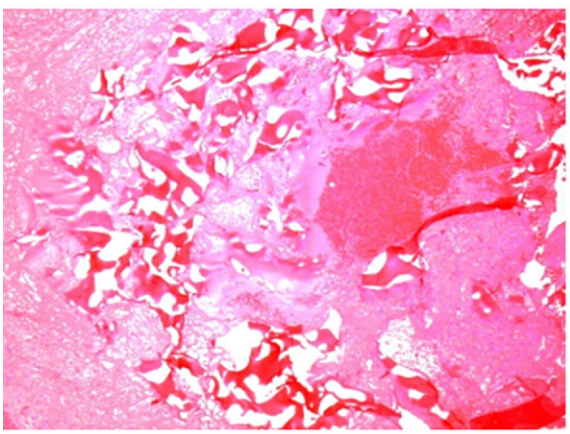
The deepest tissue typically removed during operative debridement is the bone, which, clinically, is soft if infected and can be easily removed with a rongeur. Osteomyelitis requires treatment and will impair a wound from healing, regardless of the wound type. In this study, acute osteomyelitis (Fig. 3A) was seen in between 33% and 39% of PUs and DFUs, respectively. In the senior authors' experience, deep debridement of infected bone rarely resulted in inhibition of soft tissue growth. Although bone is not routinely exposed in a VU, 29% of specimens that did contain bone were positive for osteomyelitis. This finding is suggestive that more debridement is necessary, with concomitant an-



A



B



C

Figure 3. (A) Acute osteomyelitis seen with central stripe of light pink bone on hematoxylin and eosin, with infiltration of inflammatory exudates of neutrophils and histiocytes. (B) Bone interspersed with areas of fibrosis from a pressure ulcer. (C) Reactive bone, which is free of infection and is characterized by increased osteoblastic activity. Prepared with routine hematoxylin and eosin staining.

tibiotic treatment for the specific bacteria cultured from the bone.

A limitation of this study was that patients examined were not standardized with respect to the duration of their wounds or how they were treated at previous centers. Although the analysis included only the patients' first debridement at this center, it may not have necessarily been the patients' initial debridement. To rigorously validate a margin of debridement, eventual clinical outcomes, such as wound closure or amputation, must be studied in concert with the pathology results at multiple time points. Such a study is currently underway using the WEMR, which captures all the relevant variables at each and every patient visit, including pathology findings, wound area, and amputation. Another limitation is the retrospective design of the study and the fact that the findings reported were not prospectively determined. A study is currently underway to prospectively identify abnormal findings from chronic wounds to ensure that presence or absence of all findings is reported. A suggested format for such a surgical pathology template is presented in the appendix (available online).

In contrast to tumor excision, there are few objective histopathologic markers to guide the width and the depth of operative debridement in the treatment of nonhealing ulcers. The goal of sharp debridement of a chronic wound is to remove cells at the skin edge and ulcer bed that are physiologically impaired. Few reports describe the histologic abnormalities present in chronic wounds. After adequate and reproducible description of findings at the skin edge and wound bed of chronic wounds, we hypothesize that a margin of debridement can be established based on pathologic analysis of debrided tissue. Just as the surgeon trained in Moh's micrographic surgery must be both surgeon and pathologist, to excise the cutaneous lesion until a tumor-free plane is reached,[29] it is equally important for the wound surgeon to systemically examine the pathology from the wound to identify physiologically impaired cells. Once identified, these cells can be surgically removed. Because most, if not all, patients in this study were debrided more than once, using a prospectively evaluated methodology may decrease the number of debridements, increasing the efficacy of each one. Although it is surgical dogma that an adequately aggressive debridement removes all devitalized tissue, this study shows that even in experienced hands, hyperkeratosis, fibrosis, and even acute osteomyelitis exist at the debridement margins and in the depths of chronic wounds. More studies are needed and underway to test whether the removal of such abnormal tissue improves healing, decreases sepsis, and prevents amputations in PUs, DFUs, and VUs.

Author Contributions

Study conception and design: Golinko, Tomic-Canic, Brem
Acquisition of data: Joffe, DeVinck, Chandrasekaran
Analysis and interpretation of data: Golinko, Joffe, DeVinck, Stojadinovic, Barrientos, Vukelic, Tomic-Canic, Brem
Drafting of manuscript: Golinko, Joffe, Chandrasekaran, Brem
Critical revision: Joffe, DeVinck, Stojadinovic, Barrientos, Vukelic, Tomic-Canic, Brem

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Appendix:

Prospective Template for Histopathology of Chronic Wounds

The following table represents the next step toward defining the margin of debridement of chronic wounds. In addition to the usual pathology report that appears in the medical record, the pathologist may use this table to circle the various findings observed in the wound specimen as soon as it is received. These sheets are then collected and the data entered into the WEMR. In this prospective fashion, statistical analysis can reveal which histopathology variables relate to clinical outcomes such as healing rate and amputation.

Similar to the observational tables (Tables 1 to 3), this prospective template includes the major tissue levels encountered in routine debridement of chronic wounds. Several differences include orientation of the skin edge, ie, the portion closest to the center of the wound, the inner edge, and the portion furthest away, the outer edge. This distinction orients the specimen for the pathologist and may allow for easier identification of the "negative margin" after prospective statistical analysis. In addition, included are variables for infection such as presence or absence of bacterial colonies or fungus, which are known to inhibit wound healing. The template provided here is by no means comprehensive, but may serve as a starting point from which to prospectively address which histopathology findings are important prognostic indicators of healing and amputation in patients with chronic wounds.

Skin: inner edge/skin outer edge	Pathology Findings Present			
Epidermis present	Yes	No		
Hyperkeratosis/parakeratosis	Yes	No		
Hyperproliferation (acanthosis/thickened epidermis)	Yes	No		
Bacterial colonies	Yes	No		
Necrosis	Yes	No	Fat	Suppurative
Giant cell reaction	Yes	No		
Hemosiderin	Yes	No		
Fibrinous exudate	Yes	No		
Malignancy	Yes	No		
Fungus (GMS stain)	Yes	No		
Superficial tissue (wound bed)				
Epidermis present	Yes	No		
Hyperkeratosis/parakeratosis	Yes	No		
Hyperproliferation (acanthosis/thickened epidermis)	Yes	No		
Bacterial colonies	Yes	No		
Necrosis	Yes	No	Fat	Suppurative
Giant cell reaction	Yes	No		
Hemosiderin	Yes	No		
Fibrinous exudate	Yes	No		
Malignancy	Yes	No		
Fungus (GMS stain)	Yes	No		
Deep tissue/muscle/tendon				
Fibrosis (dense collagen)	Yes	No		
Granulation tissue	Yes	No		
Fibrin	Yes	No		
Cellularity (fibroplasia)	Yes	No		
Necrosis	Yes	No		
Inflammation	Acute	Chronic	Both	Neither
Bone				
Osteomyelitis	Acute	Chronic	Both	Neither
Reactive changes	Yes	No		
Fibrosis	Yes	No		
Blood vessels				
Fibrin cuffs	Yes	No		
Venules	Yes	No		
Capillaries	Yes	No		

GNS, Gomori methenamine silver stain; WENR, Wound Electronic Medical Record.