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Wound Healing and Infection

Renee Genova
J. Tracy Watson
Bruce A. Kraemer

INTRODUCTION

Restoration of a patient's function, pain control, promotion of healing while minimizing potential complications such as infection and nonunion are fundamental goals in the management of the orthopaedic trauma patient. While some clinical pictures appear quite straightforward and evolve uneventfully, it is essential that the treating surgeon have a thorough understanding of the many factors involved in each step along the path to healing. He or she must be able to identify the modifiable risk factors in each individual case to optimize treatment so that outcomes may be maximized. It is also important to remember that fractures are as different as the individuals who present with them and taking a cookie cutter approach to all comers will likely leave the fracture, the patient, and the surgeon wanting.

WOUND HEALING

BASIC PATHOPHYSIOLOGY OF WOUND HEALING

Wound healing is an intricate process that can be summarized by dividing the cascade into four stages:

1. Hemostasis
2. Inflammation
3. Proliferation (granulation, vascularization, wound closure)
4. Remodeling

Each stage is affected by enzymes, growth factors, inflammatory cells, and signals both from the microenvironment in addition to our interventions.[1] Proper nutrition is required for our basic physiologic function, and these requirements are increased with the additional energy involved in wound healing. Oxygen is essential for normal physiology, and like nutrition, there are increased oxygen needs in the setting of wound

healing.[1] In addition to the trauma itself, peripheral arterial disease, infection, diabetes, and tension on the tissues can all negatively affect oxygenation limiting wound healing potential.[1]

WOUND HEALING IN ORTHOPAEDIC TRAUMA

In addition to rudiments of basic wound healing, additional principles must be considered when addressing injuries and wounds in the orthopaedic trauma patient. These include, but are not limited to, open fractures, closed crush injuries, injuries to the distal lower extremity and associated fracture blisters, zone of injury, and internal fixation.

Fracture blisters are often present in the setting of pilon, tibial plateau, and calcaneus fractures and may continue to evolve along with swelling for days following the injury. Surgical incisions made through significant soft-tissue swelling or fracture blisters can lead to potentially preventable postoperative wound complications. Two types of fracture blisters are recognized: clear fluid–filled blisters and blood-filled blisters.[2,3] Both blister types are a result of the shearing forces experienced at the time of injury resulting in cleavage between layers of the dermal tissue. A clear fluid blister contains sterile scattered areas of retained epithelial cells, which can lead to faster reepithelialization and less morbidity than a hemorrhagic blister. A blood-filled blister (Figure 4.1A and B) may represent a more significant injury involving deeper layers of the dermis and is more likely to heal with scar formation rather than the uncomplicated reepithelialization seen with sterile fracture blisters.[4]

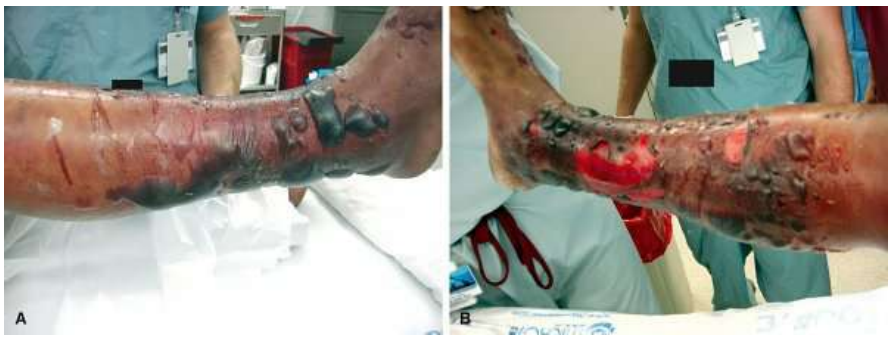

FIGURE 4.1 **A** and **B**, Hemorrhagic blisters indicating a more severe injury with necrosis of the superficial epidermal layers and deep tissue damage, as a result of internal degloving. Any invasive surgical approach should be delayed until soft-tissue recovery and reepithelization of the blisters have occurred.

Severe contusion or blister formation is a direct factor contributing to the development of a wound complication.[5] Blisters are a hard sign indicating deep tissue involvement, and open surgical management is avoided until the blisters have

resolved.[4] Varela et al[3] examined 51 patients with fracture blisters and found that the average time until the fracture blister was noted on clinical examination was 2.5 days after injury.

Blister care includes application of a nonadherent dressing with or without aspiration of the blister fluid and is followed by fracture reduction and application of a compressive dressing. Even when temporary spanning fixation has been utilized, a compressive dressing with multiple layers should be applied. This provides circumferential compression and minimizes the shearing effect on the injured tissue layers, which begins at the bone and progresses outward. The circumferential compression prevents delamination of the fascia from the muscle, the subcutaneous tissue from the fascia, and finally the epidermis from the dermis.

The wrinkle test is a reliable clinical sign used to determine skin integrity and suggests the resolution of soft-tissue edema. Presence of wrinkles and the ability to "pinch" up skin demonstrates that the interstitial third spacing of fluid is resolving and will allow the skin to be mobilized, enabling closure without undue tension. An additional adjunctive measure to help the soft tissues recover before surgery is the use of a pulsatile A/V foot pump compressive device placed in combination over a multilayered compressive dressing. The effectiveness of this technique is described in a consecutive series of 64 closed ankle fractures that were managed using an A/V foot pump system incorporated into the compressive dressing before surgery.[6] Use of this preoperative soft-tissue protocol was associated with the surgeon's ability to evaluate injury and expedite management. They found their soft-tissue complications and wound infections were also significantly reduced with the use of preoperative A/V compression foot pumps.

POSTOPERATIVE SOFT-TISSUE MANAGEMENT

Respecting the soft-tissue envelope is essential and should be considered a priority from the initial steps in management of a fracture until the patient is considered healed and appropriate for discharge. Management of the postoperative soft tissue starts preoperatively; it is critical that the appropriate surgical approach be utilized, with judicious incisions minimizing the undermining of skin flaps. Proper fixation with smaller implants that minimize fragment stripping and allow minimally invasive surgical techniques to be carried out is of primary importance during the fixation strategy. Meticulous soft-tissue handling is mandatory to minimize soft-tissue complications. Gentle retraction with smooth retractors, avoidance of crushing the skin margins with forceps, use of shorter tourniquet times, and frequent irrigation of the tissues are all tenets of soft-tissue protection during surgery.[7] Minimizing operative time, specifically time the incisions are "open," has been found to be a primary predictor of post-op wound infection.[7] Open fractures, elevated postoperative glucose

levels (≥125 mg/dL), and a surgery duration of more than 150 minutes with the wound "open" were associated with an increased risk for surgical site infection after open reduction and internal fixation of pilon fractures.[8] Thus, it is critical to perform thorough pre-op planning and develop a surgical tactic *before* incisions are made.

After all the planning and meticulous surgical technique, the closure should not be relegated to the most junior individual in the operating room. A tension-free closure is necessary to avoid wound compromise. If this cannot be obtained, the wound should be left open and later closed secondarily or closed with either a skin graft or a muscle flap. When treating pilon fractures, Leone advocates primary closure of the tibial incision, with delayed closure of the fibular incision or delayed split-thickness skin grafting of the fibular wounds to achieve coverage of the tibial component.[9]

Soft-tissue complications should be identified and treated early. McFerran et al[10] reported an overall local complication rate of 54%, with 40% of patients requiring an unplanned reoperation. Most of these complications occurred within 3 weeks of surgery; only two occurred more than 40 weeks after the index procedure. The authors concluded that the majority of complications were soft tissue initiated.[11]

WOUND MANAGEMENT

The management of a wound complication requires mature clinical judgment, and one should not live in denial and avoid immediate treatment. The best chance to avoid significant morbidity is to act aggressively as the situation requires. Superficial skin necrosis can be treated with local wound care, limb elevation, and close observation. If mild cellulitis with erythematous margins about the wound is present, the patient should be treated with oral antibiotics. If the cellulitis does not respond promptly or if a more significant cellulitis extending away from the margins of the wound is present, the patient should be admitted for intravenous antibiotics. Cultures taken from superficial skin drainage are historically unreliable and generally do not reflect the pathogenic infecting organism that may be deep to the incision.

At this time, negative-pressure wound therapy (NPWT) can be initiated and antibiotic therapy should be continued until all marginal erythema has resolved. However, if superficial skin loss results and the deep tissue or peritenon is intact, and deep tissue cultures are culture negative, these areas can be simply covered with a split-thickness skin graft once a healthy bed of granulation tissue has developed with the use of NPWT.

Full-thickness wound dehiscence generally results in immediate contamination of the underlying hardware and bone, is a very different situation from superficial wound necrosis, and requires aggressive debridement in the operating room followed by soft-tissue coverage as soon as feasible. This clinical scenario usually requires a rotational flap or free tissue transfer and should be performed before the onset of deep infection.

During the initial debridements, deep tissue cultures should be obtained to rule out deep infection and guide specific antibiotic management. Additionally, the internal fixation should be visualized and its structural continuity and stability evaluated. If it is determined that the hardware provides stable fixation, it should be retained and soft-tissue coverage initiated. A 3- to 6-week course of intravenous antibiotics is recommended based on deep tissue culture results.

However, if at any time fixation demonstrates any instability, it should be removed and replaced with a stable fixation construct. Fracture reduction may be lost, and a late reconstructive procedure may be necessary once the soft tissues have healed. If deep cultures are positive, the situation is much more complex and a staged reconstruction for a potentially infected nonunion should be undertaken.

Negative-Pressure Wound Therapy

NPWT, frequently referred to as "vacuum-assisted closure" or "VAC," has recently demonstrated widespread use from management of decubitus ulcers to its use in postoperative wounds in many of the surgical subspecialty patient populations including orthopaedic trauma.

The NPWT system consists of three components: (1) porous dressing (sponge); (2) occlusive seal adhesive; (3) vacuum device with connector that together create the subatmospheric pressure environment that defines NPWT.

There exist a variety of sponge options, each with its own characteristics and unique contribution to the specifics of the NPWT environment. The most commonly used porous dressing (or sponge) in orthopaedic trauma surgery is the dry black sponge for its hydrophobic, reticulated large pore size foam, which provides for a more adherent application and significantly increased granulation and perfusion than a premoistened polyvinyl alcohol foam with smaller size pores.[12]

This therapy can be applied directly over high-risk surgical incisions that have been closed, referred to as an "incisional VAC." Placing such an incisional VAC on the surgical incision used for open reduction and internal fixation of a pilon fracture at the time of closure has been shown to reduce the risk of developing acute dehiscence and wound infection.[13] Another trial evaluated wound dehiscence and infection after high-risk lower extremity trauma. The relative risk of developing an infection was 1.9 times higher in standard dressing patients compared to patients treated with NPWT.[14,15]

Studies have demonstrated the stimulatory effects that NPWT has on local angiogenesis to increase local blood flow, and the ability to reduce the surface area of the wound as well as to increase the induction of cellular proliferation. The current data does not demonstrated its ability to reduce wound edema or the clearance of wound bacteria.[16]

Hyperbaric Oxygen Therapy

Healthy cells of nontraumatized tissues have a baseline oxygen requirement; naturally, cells of traumatized tissues have increased oxygen requirements compared to cells of nontraumatized tissues. Unfortunately, the same traumatized environment that increases the oxygen requirement of these cells is the very environment that decreases the oxygen available to them secondary to the traumatically induced edema.[17] In addition to limiting the oxygen available to the tissue, edema also diminishes the microcirculation that is integral in tissue healing and infection prevention and treatment in these traumatized tissues.[17] The downstream effect is growth of bacteria in an environment with limited exposure to circulating blood and antibiotics within it.

Specifically, fibroblast function is dependent on an oxygen tension of 30 mm Hg; therefore in the setting of decreased oxygen tension as can occur in the setting of a soft-tissue injury, these cells cannot mobilize and produce collagen matrix required for neovascularization and wound healing.[18]

Hyperbaric oxygen therapy (HBOT) has applications in diving medicine, carbon monoxide poisoning, gas gangrene, effects of radiation, and chronic wounds in the diabetic patient.[19] HBOT in conjunction with interdisciplinary wound care to decrease the risk of amputation in a patient with a diabetic foot ulcer is supported by a high level of evidence.[19] Animal models have demonstrated HBOT to minimize necrosis of muscle and reduce the edema in compartment syndrome,[20] and Radonic et al[21] suggested that HBOT decreased the rate of amputation in their military population sustaining combat injuries with prolonged ischemic periods. Others have also noted similar results in the setting of extensive bony and soft tissue injuries.[22]

Extracellular Matrix Materials

Extracellular matrix (ECM) materials such as urinary bladder matrix-extra cellular matrix (UBM-ECM) and dermal regeneration template (DRT) may facilitate definitive soft-tissue reconstruction by establishing a durable dermallike soft-tissue base acceptable for second-stage wound and skin coverage. Using these biomaterials, a new dermal layer can be established for second-stage wound and skin coverage options.[23] This approach may be suited in patients who are often poor surgical candidates for more advanced reconstructive procedures. Two materials are currently FDA approved. The first is an acellular, non–cross-linked, ECM scaffold derived from porcine bladder basement membrane. The material is applied in powder, single or multilayer sheets.[23] The ECM is typically applied in the operating room at the time of initial operative debridement. The UBM-ECM products have been found to facilitate healing despite the presence of exposed hardware and positive bacterial cultures, provided that all grossly devitalized bone has been removed (Figure 4.2A).[24] Once a bed of granulation tissue is achieved, the acellular dermal templates are applied directly over the clean wound (Figure 4.2B). Reapplication of the matrix may be required until a dermallike layer is

established. Wounds can then heal secondarily or combined later with split-thickness skin grafting and NPWT (Figure 4.2C). Use of these extracellular porcine bladder matrices gives these patients additional options as they are combined with delayed skin grafting, local pedicle flaps, adjacent tissue rearrangements, and/or free tissue transfers.[25]

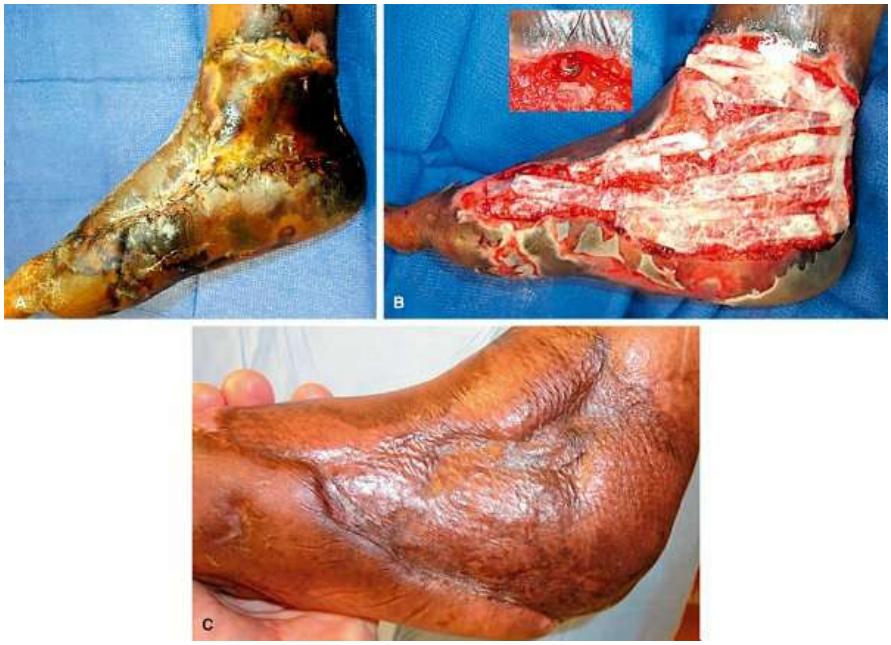

FIGURE 4.2 **A**, Soft-tissue necrosis secondary to a crush injury to the foot. This resulted in significant soft-tissue loss down to the superficial fascia of the foot. **B**, Following radical soft-tissue debridement, an acellular matrix has been placed directly over the deep tissues to develop a durable dermal layer that can eventually be skin grafted. Note, this matrix will facilitate granulation tissue formation even over exposed hardware (window). **C**, Split thickness skin grafting occurred over the reconstructed dermal layer, and this composite grafting technique provides durable soft-tissue covering with dermal and epidermal layers as opposed to skin grafting directly over muscle, bone, or fascia.

DRT Integra® Meshed Bilayer Wound Matrix (Integra Life Sciences Corporation), the second material available, is a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan and a semipermeable polysiloxane (silicone) layer. The meshed bilayer allows drainage of wound exudate and provides a flexible adherent covering for the wound surface. The collagen-glycosaminoglycan biodegradable matrix provides a scaffold for cellular invasion and capillary growth. Secondary procedures can be carried out once the basement tissue layer has been established.

Flap Coverage

The principle of aggressive wound debridement with early free flap wound coverage has dominated the management of wounds involving the distal third of the tibia and

ankle. Free flap coverage is the workhorse coverage for those areas of significant soft-tissue loss secondary to massive wound necrosis. These are primarily used in cases of infected nonunion where eradication of infection requires radical debridement of involved bone and soft tissue. Unfortunately, the area most difficult to cover with muscle flaps is the lower third of the leg (Figure 4.3). The advent of fasciocutaneous flaps has stimulated great interest in the cutaneous circulation of the lower extremities and in alternatives to traditional, proximally based free flap procedures. Rather than sacrificing the whole vascular axis in the process of transferring a flap, flaps can be based on a single septocutaneous perforator of the tibial or peroneal vessels.[26]

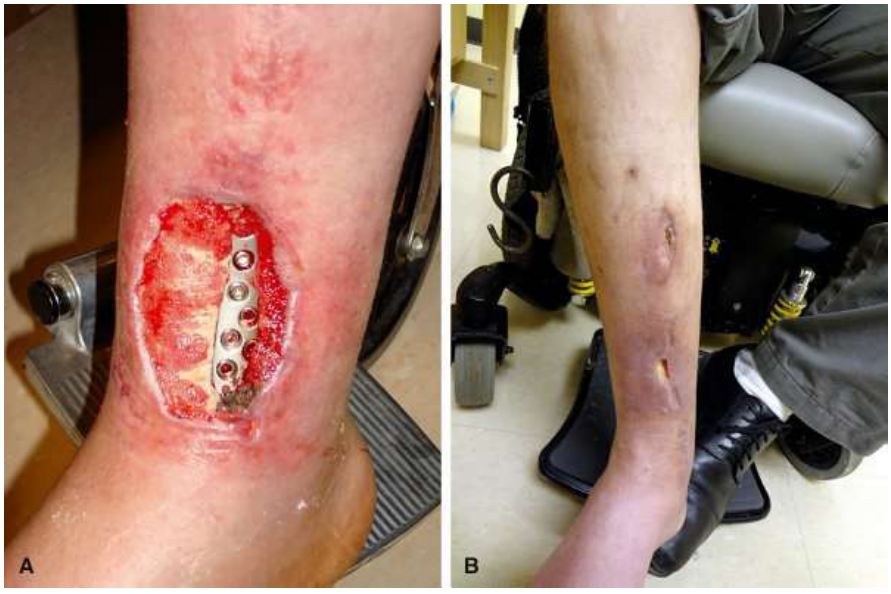

FIGURE 4.3 **A** and **B**, Wound breakdown over the distal third of the tibia following a medial "percutaneous" plating technique. Now exposed hardware is present. Even with limited incision techniques, this area is very sensitive to any additional surgical insult on top of the soft-tissue damage that occurs with distal third tibial fractures. This resulted in additional soft-tissue procedures to achieve competent wound closure with healthy soft tissues.

Pedicled perforator flaps have several obvious advantages over free flaps. They can be performed expeditiously, and this is particularly beneficial in the management of soft-tissue defects in multiply injured patients, the elderly, and systemically compromised patients.[27] This reconstruction can replace like-with-like, by using tissues of similar texture, thickness, pliability, and color. This method avoids the complexity of multiple surgical sites, the need for special instrumentation, and the requirement for transfer of patients to specialty centers with the extra costs associated with free flaps and microsurgery.[27] Local flap surgery limits the scars and morbidity to one extremity. These are ideally suited to the smaller defects that result from wound dehiscence or wound breakdown resulting from the limited incisions currently used for pilon

fixation.[28]

Pedicled perforator flaps have several potential disadvantages, particularly when used for major posttraumatic soft-tissue defects. The principal criticism is that the flap is raised within the zone of injury and its vascularity could be compromised. Appreciation of the vascular basis of such flaps and adequate assessment of degloving minimizes this risk. Incorrect raising of local skin flaps can interrupt superficial veins and cutaneous nerves, leading to edema and neuromata. Free flaps can be tailored to suit massive or irregular skin defects, whereas the design of a pedicled flap tends to be limited by the local anatomy and availability of skin and wound orientation. Local flaps can leave a significant cosmetic defect of the donor site, which may be difficult to camouflage.[28]

Failure of a local perforator flap leaves alternative methods including free flaps. As in free flaps, there is donor site morbidity. However, because the source artery and underlying muscle are preserved, morbidity is limited to only one region. For defects less than 6 cm wide, the donor site can be primarily closed.[29] In women, a problem can be the cosmetic deficit at the donor site. Another potential problem if the perforator is within the zone of injury is that the viability of the flap may be compromised. With few options, donor site defects may have to be accepted. Poor flap candidates may benefit from minimally invasive wound management such as NPWT and matrix materials.

INFECTION

PATHOPHYSIOLOGY AND RISK FACTORS OF SURGICAL SITE INFECTION

It is believed that infection of surgical sites are acquired intraoperatively, making the sterile techniques in the operating room integral in the prevention of this potentially devastating complication.[30] It is therefore vital that the aseptic techniques such as hand washing, skin preparation, and sterilization procedures are strictly adhered as the first step to minimize the risk of a surgical site infection.[31]

Risk factors for infection can be either modifiable or not. Modification and optimization of many patient factors during the perioperative period may have a positive impact in preventing postoperative infections in orthopaedic trauma patients. These modifications include, but are not limited to, reversing malnutrition, nicotine cessation, tapering high-dose corticosteroid therapy, and maximizing oxygen delivery to the tissues.[30]

Often associated with malnutrition, a zinc deficiency in a patient makes them more likely to develop complications with wound healing. Supplementing a patient's zinc to reach serum levels above 95 μg/dL is associated with a significantly lower risk for postoperative wound complications.[32]

The detrimental effects nicotine has on our human physiology via a variety of

mechanisms including many that negatively impact wound healing have been born out in the literature.[32] More important, however, is that smoking cessation decreases the risk of wound complications and fracture nonunion; the magnitude of the decrease in risk is commensurate with the duration of the smoking cessation.[32] It has been well established that hyperglycemia in a diabetic patient undergoing total joint replacement, spine surgery, and fracture surgery is associated with significantly increased rates of postoperative infections and other complications.[33-35] Recent data demonstrate that an increased perioperative blood glucose in nondiabetic patients undergoing operative fixation of a closed fracture was associated with an increased risk of surgical site infections.[36,37] The elevated blood glucose in these nondiabetic patients is attributed to the well-established phenomenon of stress-induced hyperglycemia. Identification of hyperglycemia in a nondiabetic trauma patient is therefore crucial as is the treatment of it with a goal perioperative blood glucose level less than 200 to 220 mg/dL (depending on the study) to statistically and predictably decrease the risk of a surgical site infection.

MANAGEMENT OF ORTHOPAEDIC INFECTION

Understanding the pathophysiology of infection in the setting of a fracture treated with open reduction and internal fixation is essential to appropriately treat the infection. Specifically, the formation of a biofilm establishes a sophisticated environment with multiple impediments to eradicating the infection including a hydrophobic structure that functions as a semi-impermeable barrier to the very antibiotic intended for the microbes of the biofilm.[38] For this and other reasons, simply administering even targeted intravenous antibiotics alone will not cure the musculoskeletal infection in the setting of retained hardware.

Therefore, to eradicate the infection, a methodical approach that addresses the pathogen, host factors, bony, and soft-tissue deficiencies is required including[38]:

1. Thorough and scrupulous debridement
2. Dead-space management
3. Soft-tissue and bone reconstruction using principles of the reconstruction ladder

Whether to remove the hardware can be a difficult decision, especially in the setting of a fracture that has not yet healed but has maintained stable fixation in the setting of an infection. Controversy exists as to if all hardware should be removed and the infection completely eradicated, or if merely suppressing the infection and maintaining stable fixation is more optimal to obtain fracture union.

Acute or Subacute Infection With Stable Hardware

When dealing with orthopaedic implant–related infections, the knee-jerk recommendation of nonsurgical consultants is often to remove all hardware, obtain deep cultures, and administer antibiotics. This is partially correct. Cultures are helpful,

antibiotics are essential, but removal of stable, functioning hardware in the setting of the acutely infected fracture should be resisted resolutely. Although it is well known that the presence of inanimate material surfaces increases the risk of infection, lowers the inoculum necessary to cause infection, and reduces the chances of successful treatment, long-standing clinical experience teaches that skeletal stability reduces the infection rate.[4,39] This reduction is supported by the results of animal studies.[40,41] The mechanism by which instability promotes infection is not clear but may have to do with interference with revascularization of injured tissues, ongoing tissue damage, or increased micro–dead space. Although instability seems to interfere with the resolution of infection, the presence of infection does not necessarily prohibit bone healing. A logical strategy is to maintain stable internal fixation, which will facilitate union, and plan for hardware removal later if infection persists after the bone is healed.

For the treatment of acutely infected fractures, Berkes reported a 75% rate of fracture union and resolution of infection utilizing a standardized protocol of operative debridement, retention of *stable* fracture hardware, and culture-specific IV antibiotics (Figure 4.4A-C). Factors that were predictors of treatment failure included the injury being an open fracture (P = .03), the presence of an intramedullary nail (P = .01), a high association with smoking, and any infection with *Pseudomonas* species or other gram-negative organisms.[42]

FIGURE 4.4 **A**, Eighteen days postoperative wound development of purulent drainage after open reduction and internal fixation of a periprosthetic midshaft femur fracture. **B**, At debridement, necrotic bone and soft tissue with gross purulence were discovered. **C**, Fracture construct appears to impart excellent stability. Hardware was retained following removal of necrotic bone and soft tissue. **D** and **E**, The defect was filled with antibiotic cement and competent lateralis flap rotated over the defect to achieve wound closure. **F**, A well-developed pseudoperiosteal membrane developed around the spacer and began bone incorporation medially along the membrane itself. **G** and **H**, At the time of grafting, the fixation was exchanged for a new longer plate. The spacer was carefully removed, preserving the membrane and developing bone. Reamer-irrigator-aspirator grafting was placed into the well-developed defect, and rapid consolidation occurred.

Other authors have also identified factors that contribute to the successful salvage of acutely infected fractures. These include the maintenance of stable hardware, and that the time of surgery to infection diagnosis is less than 2 weeks.[43]

Another factor for successful salvage is the ability to achieve a thorough debridement of the fracture construct. If a collection of pus exists around an implant or under a flap or incision, it must be thoroughly drained. Incisions made for irrigation and

debridement of infection should rarely be closed and should be placed carefully to avoid exposing hardware, bone, tendon, or neurovascular structures. If these are unavoidably exposed, consideration should be given to flap coverage of the wound. The ability to achieve competent wound closure is another predictor of successful salvage. The VAC (Kinetic Concepts, Inc.) dressing can be used while awaiting definitive coverage (Figure 4.5A-C).

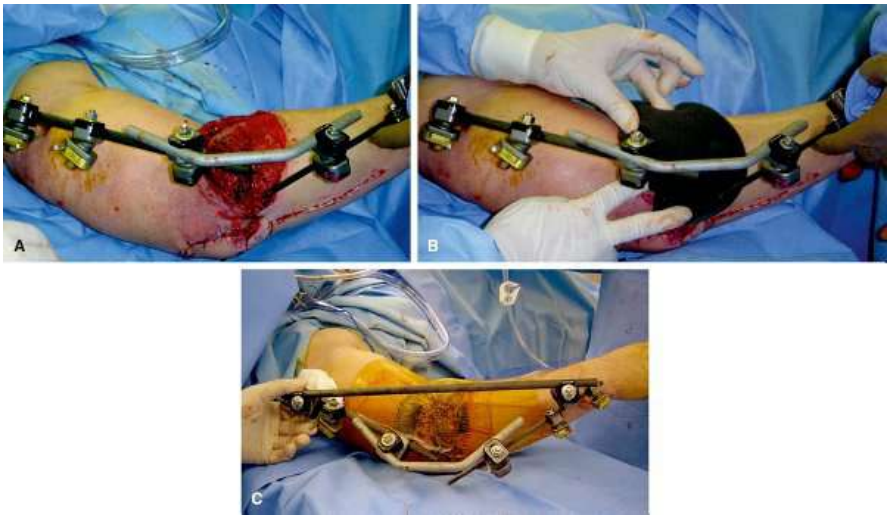

FIGURE 4.5 **A-C**, Open elbow wound following severe olecranon fracture dislocation. Negative pressure sponge is cut and shaped to cover the wound and wound margins. Sponge is then sealed over the wound and a negative pressure obtained following an occlusive overwrap dressing.

As mentioned previously, culture-specific antibiotic treatment should be standard when treating these acutely infected stably fixed fractures. Furthermore, consideration to adding rifampin to culture-proven staphylococcal infections should be strongly considered. A randomized controlled trial to evaluate the utility in adding rifampin to conventional culture-proven staphylococcal infection associated with stable orthopaedic implants in patients with symptoms of infection that were acute or subacute in duration demonstrated a 100% cure rate in the group treated with ciprofloxacin-rifampin compared to the 58% cure rate in the group who received ciprofloxacin-placebo.[44]

In a study by Rightmire et al,[45] outcomes in patients with acute infections after fracture repair managed with retained hardware were reviewed. They evaluated the effectiveness of treating these patients with irrigation, debridement, and antibiotic suppression in the setting of retained hardware. A successful outcome was defined as a patient obtaining fracture union with original hardware in place.[45] There was a 68% success rate with an average of 120 days until fracture healing, and 36% of these patients went on to present with reinfection. The majority of the infected fractures that failed debridement and antibiotics with retained hardware failed within 3 months from the time of initial surgery. Patients who smoked were at a significantly higher risk of