Abstract

Negative-pressure wound therapy (NPWT) has become an important adjunct to the management of traumatic wounds and surgical incisions related to musculoskeletal trauma. On the battlefield, this adjunct therapy allows early wound management and safe aeromedical evacuation. NPWT mechanisms of action include stabilization of the wound environment, reduction of wound edema, improvement of tissue perfusion, and stimulation of cells at the wound surface. NPWT stimulates granulation tissue and angiogenesis and may improve the likelihood of primary closure and reduce the need for free tissue transfer. In addition, NPWT reduces the bacterial bioburden of wounds contaminated with gram-negative bacilli. However, an increased risk of colonization of gram-positive cocci (eg, Staphylococcus aureus) exists. Although NPWT facilitates wound management, further research is required to determine conclusively whether this modality is superior to other management options. Ongoing research will continue to define the indications for and benefits of NPWT as well as establish the role of combination therapy, in which NPWT is used with instillation of antibiotic solutions, placement of antibiotic-laden cement beads, or silver-impregnated sponges.

Negative-pressure wound therapy (NPWT) evolved based on the need for coverage and drainage of traumatic soft-tissue wounds and defects associated with open fractures as well as on early observations of the effect that polyurethane sponges had on soft-tissue granulation.¹

The first clinical report on NPWT described the use of a polyvinyl alcohol sponge embedded in a soft-tissue defect, sealed with polyurethane drape, and connected to drains via percutaneously placed tubes.¹ Subsequent studies analyzed the use of NPWT with polyurethane ether foam for management of acute and chronic wounds and the use of a vacuum pump that allowed adjustment of vacuum magnitude and selection of continuous or intermittent negative pressure.²,³ All NPWT systems use an open-pore reticulated foam, an occlusive semipermeable dressing, and a suction device with a fluid receptacle (Figure 1). Several commercially available NPWT systems are described in Table 1.

Components of a NPWT System

Open-pore Sponge

Commercially available sponges are made of either polyurethane ether or polyvinyl alcohol. The open-pore structure is a key characteristic of...
Use of negative-pressure wound therapy in orthopaedic trauma

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sponges used in NPWT. This structure allows negative pressure to be transferred across the entire sponge-wound interface from a suction source connected to the surface of the sponge. Basic science studies have shown that the pore size of polyurethane ether sponges (400 to 600 µm) maximizes fibrovascular tissue ingrowth; thus, these sponges are used preferentially to manage soft-tissue defects in which granulation tissue is desired.4-6 However, based on anecdotal experience, polyurethane sponges can lead to tissue ingrowth; therefore, they are not recommended for use in areas with exposed tendons, nerves, and viscera. In this setting, saline soaked polyvinyl alcohol sponges are indicated because their pore size (60 to 270 µm) is less prone to tissue ingrowth,7 thereby leading to less bleeding and pain during dressing changes8 (Figure 2).

Semiocclusive Dressing
Adhesive drapes are required to seal the wound to allow production of an effective vacuum. Semiocclusive membranes are used to avoid protein loss and wound desiccation while isolating the wound from nosocomial contaminants. Most manufacturers provide precut adhesive polyurethane drapes with commercial NPWT systems. At our institution, we have found that the use of iodophor-impregnated drapes may be beneficial because they can be cut to accommodate various wound sizes and can be used to seal around external fixation devices (Figure 3). Furthermore, basic science studies have shown that iodophor-impregnated drapes achieve prolonged control of bacterial colonization of the skin than do conventional adhesive drapes. In addition, when used in combination with an iodophor-alcohol preparation, these drapes have more reliable adhesion to skin.9,10 To our knowledge, studies on the clinical impact of this decrease in bacterial counts have not been performed.

Negative Pressure Source
Contemporary commercial NPWT systems rely on vacuum pumps that can be regulated according to magnitude and intermittency of negative pressure. Using an animal model, Morykwas et al3 showed that applying −125 mm Hg of pressure to a wound using a vacuum-assisted closure (VAC) device had the greatest effect on formation of granulation tissue. This effect was further increased when suction was intermittently generated for 5 minutes at 7-minute intervals (ie, 5 minutes “on” and 2 minutes “off”). Furthermore, a fourfold increase in blood
flow was observed in tissues surrounding a wound when the VAC device was set at −125 mm Hg. At negative pressures ≥400 mm Hg, blood flow fell below baseline. Intermittent negative pressure generated a reactive increase in blood flow for at least 2 minutes during “off” times.

With continuous negative pressure, granulation tissue increased by 63% compared with baseline controls; however, granulation increased by 103% with intermittent negative pressure.3

Different pressure settings are recommended based on clinical indication. For management of acute traumatic wounds, negative pressure of 125 mm Hg at intermittent cycles is recommended.8,11-14 In the setting of incisions at risk of breakdown and/or infection, such as those with prolonged drainage or those located in anatomic areas with a higher like-
Intraoperative photographs demonstrating use of a negative-pressure wound therapy system for management of an infected surgical wound. A, The wound had exposed tendons and required serial surgical débridements. B, A polyvinyl alcohol sponge is cut to the size of the wound and is used to protect the exposed tendons. C, Following placement of the initial polyvinyl alcohol sponge, a polyurethane ether sponge is cut to fit. D, The polyurethane ether sponge is carefully placed, avoiding overlap with intact wound edges. The skin is then prepared with an alcohol-based iodine solution. E, Five-inch strips of iodophor-impregnated self-adhesive drape are applied to the incision to obtain full occlusion of the wound and an airtight seal that will allow effective vacuum generation. F, An opening is cut into the surface of the occlusive drape to expose the pores of the sponge. G, The adhesive connector of the evacuation tube is sealed onto the opening. H, A vacuum is generated and adequate collapse of the sponge can be visualized. Potential air leakage should be corrected with the use of additional adhesive foil.

Mechanism of Action

In an extensive systematic review of the literature on NPWT, Orgill et al6 described the four primary effects of NPWT: wound contraction, stabilization of the wound environment, decreased edema and removal of wound exudates, and microdeformation. These effects allow NPWT to speed wound healing; increase blood flow around wounds; improve wound bed preparation for subsequent closure or coverage; and change wound biochemistry, bacterial burden, and systemic response.

Wound Contraction

After traumatic or surgical skin disruption, the tensile forces of the surround-
ing soft tissues can lead to wound gapping. Prolonged wound gapping leads to soft-tissue contraction, thereby jeopardizing the capability to obtain primary wound closure, even in the absence of soft-tissue loss. NPWT exerts a contracting effect on the wound that pulls the edges together6 (Figure 4). Therefore, the possibility of delayed wound closure is increased and the need for soft-tissue transfer is reduced.

**Stabilization of Wound Environment**

Accumulation of fluids and the repetitive changes required with standard wet-to-dry (WTD) dressings may lead to an increased risk of infection. In contrast, NPWT continuously drains excess fluid with its associated proteins and electrolytes, thereby maintaining oncotic and osmotic gradients between the wound bed and surrounding soft tissues. Furthermore, the presence of an occlusive dressing prevents wound desiccation, thereby avoiding scab formation and enhancing granulation.17

Thermal insulation is a less-studied effect of NPWT. When a fluid-saturated sponge is collapsed, it is expected to yield thermal conductivity similar to that of soft tissue of a similar thickness. Furthermore, loss of water vapor and convective heat transfer is minimized with NPWT.6 This aspect is especially important in patients with burn wounds over an extensive body surface area, and it can play a role in the management of large traumatic wounds and treatment of the physiologically unstable polytraumatized patient.

**Microdeformation**

As suction induces interstitial fluid flow through the extracellular collagen matrix, secondary mechanical strain leads to cellular microdeformation. Based on bone and tendon physiology, it is well known that mechanical loading is essential in regulating tissue growth, repair, and remodeling. Additionally, as dissolved ions in the extracellular fluid flow past opposing charged glycoproteins, electric fields are created, which in turn can stimulate cellular responses3,6 and growth factor (eg, interleukin-8, vascular endothelial growth factor) synthesis.20

**Application of the VAC Device**

The polyurethane ether sponge should be cut to fit the wound. The sponge can be pressed against the wound, and wound exudates or blood can be used as a template to cut the sponge to the appropriate size. The sponge is then applied over the wound and held in place with a single staple at each corner. We prefer to cover the wound by applying the adhesive dressing in smaller strips to minimize creases. The skin is kept dry while the strips are applied, ensuring that an adequate seal
is obtained. Circumferential application of adhesive drapes should be avoided to prevent a tourniquet effect. Subsequently, a 2-cm hole is cut from the center of the dressing covering the sponge, and the suction track pad is secured over the hole. For large wounds or wounds with excessive fluid, dressing strips are applied from the nondependent to the dependent aspect of the wound.

The VAC device is connected to the track pad to allow reliable drying of the skin before final sealing. Any residual leaks are then addressed by applying additional adhesive dressing strips. We often use the continuous setting to prevent patient discomfort associated with intermittent suction. In the setting of exposed bone or tendons, a polyvinyl alcohol sponge is placed underneath the polyurethane sponge. Duration of therapy is dictated by the size and severity of the wound. The VAC device is typically left in place for 2 to 5 days before removal or repeat wound débridement and placement of a new NPWT dressing.

**Incisions**

When using a standard NPWT dressing over a surgical incision, we prefer to line the incision with thin strips of adhesive dressing just lateral to the suture or staples. A nonadherent dressing is cut into a strip approximately 1-inch wide and measuring the length of the incision and is placed over the incision. A 1-inch wide strip of polyvinyl alcohol sponge is then cut to the length of the incision and is placed over the nonadherent dressing, while avoiding direct contact with the skin. Finally, an occlusive dressing is placed over the polyvinyl alcohol sponge, and continuous suction is applied at \( -50 \) mm Hg. NPWT is discontinued after 2 to 5 days.

**Split-thickness Skin Graft**

When placing a NPWT dressing over a split-thickness skin graft (STSG), we apply a single sheet of nonadherent dressing to the wound to provide a barrier between the STSG and the polyurethane sponge. This prevents graft ingrowth into the sponge and subsequent disruption of the graft during sponge removal. Alternatively, a polyvinyl alcohol sponge can be used. We typically use \( -75 \) mm Hg of continuous suction when using NPWT for STSGs, and we leave the dressing in place for 5 to 7 days. The dressing is then removed at the bedside or in clinic.

**Clinical Indications**

NPWT was originally used to improve staged management of open fractures with associated soft-tissue defects.\(^1\) Currently, NPWT is accepted for several additional indications associated with orthopaedic trauma, including surgical incisions at increased risk of breakdown or infection, skin grafts, and infected wounds.\(^\ref{21,22}\)

**Wounds With Associated Soft-tissue Defect**

Soft-tissue management represents a key factor in successful return to function following traumatic injuries; soft-tissue coverage is needed to maintain the viability of underlying bone, joints, tendons, and neurovascular structures. In the setting of high-energy trauma, severe soft-tissue injury is common and is often associated with extensive contamination and compromised viability. Because of the high risk of infection, surgical débridement and irrigation are required to reduce bacterial load and remove devitalized tissue that may serve as soil for bacterial growth.

In the past, WTD dressings were considered the standard of care for management of soft-tissue defects and open wounds. However, WTD dressings require frequent changes, a fact that leads to increased patient pain, healthcare personnel workload, and cost. Furthermore, repeat exposure to the hospital environment increases the risk of nosocomial infection. This is of particular relevance in open fractures with marked contamination and extensive soft-tissue injury; two studies reported infection in up to \( 66\% \) of cases, most of which were caused by nosocomial bacteria.\(^\ref{23,24}\) NPWT offers a quick and reliable method for sealing the wound from nosocomial contaminants. Furthermore, by promoting local wound perfusion and drainage, definitive management can be safely delayed beyond the initial physiologic stabilization of the traumatized patient.

Several studies have compared the use of NPWT with WTD dressings. Mouës et al\(^\ref{11}\) randomized 54 patients with full-thickness wounds to treatment with NPWT or to conventional WTD dressings. No significant difference was found in wounds treated with NPWT in terms of reaching a “ready for surgical therapy” status compared with control subjects (6 versus 7 days, \( P = 0.19 \)). “Ready for surgical therapy” was defined as the presence of a clean, red, granulating wound bed as determined by an examiner who was not blinded to treatment modality. However, compared with initial wound size, wound surface reduction following treatment was \( 3.8\% \) in the NPWT group and \( 1.7\% \) in the control group (\( P < 0.05 \)). Because the examiner was not blinded to treatment modality, these results should be analyzed with caution.

Stannard et al\(^\ref{25}\) also compared NPWT with WTD dressing for management of severe open fractures. In a randomized controlled trial, the authors performed definitive closure
in patients with type A wounds, that is, those with abundant granulation tissue and no purulence. Fractures treated with NPWT (35 patients) needed 0.8 day less to achieve type A status than did those in the control group (23 patients) (3.2 versus 4 days). In addition, the infection rate in the NPWT group was significantly lower than that of the control group (5.4% versus 28%, *P < 0.024). However, the reduction in infection was not accompanied by a reduction in the need for flap coverage: 7 of 35 patients (20%) in the NPWT group received a flap compared with 3 of 23 patients (13%) in the control group. This difference may have influenced the rates of infection because flap coverage could be related to improved rates of infection and healing.

Dedmond et al23 reported the results of 49 patients with 50 type III open tibial shaft fractures managed with NPWT. Superficial infection occurred in 4 patients (8%); half of these infections were located at external fixator pin sites. Deep infection occurred in 10 patients (20%). Of these, half required either amputation or developed chronic osteomyelitis. Differential incidence of infection for types IIIA, IIIB, and IIIC open fractures was 8.3%, 45.8%, and 50%, respectively.

Duration of therapy and delay of coverage may affect the capacity of NPWT to reduce infection rates associated with open fractures. Bhattacharya et al24 retrospectively analyzed 38 patients with Gustilo grade IIIB open fractures and found an overall infection rate of 36% that varied with time to definitive coverage. Patients who underwent definitive coverage <7 days postinjury had an infection rate of 12.5%, whereas those who underwent definitive coverage after 7 days had an infection rate of 57% (*P = 0.008). This study suggests that use of NPWT should be kept to a minimum and that definitive coverage should proceed as early as possible. However, it should be noted that severe injuries have a higher risk of infection and require more frequent débridements over a longer period of time. In contrast, Steiert et al12 reported only 1 infection in 42 patients (2%) with open extremity fractures who underwent at least 3 days of NPWT before undergoing flap coverage. Mean time to definitive flap coverage was 28 days (range, 3 to 106 days). Fleischmann et al1 reported similar findings; only 1 in 15 patients (5 polytraumatized) with severe open fractures and associated soft-tissue injury developed an infection following NPWT. Average time to definitive closure or coverage was 7.25 days (range, 4 to 15 days). Based on these conflicting results, early flap coverage should be performed in a physiologically stable patient. If surgical delay is required, NPWT can be used to safely allow delayed coverage.

Currently, inconclusive evidence exists to support the superiority of NPWT over WTD dressings to avoid wound infection and flap coverage. In addition, no studies have compared NPWT with other successful treatment modalities (eg, antibiotic bead pouch [ABP]) for management of contaminated soft-tissue defects. Several factors influence complication rates associated with NPWT, including early débridement, antibiotic therapy, degree of soft-tissue and bone injury, nutritional support, and baseline patient health status. Combat-related Wounds

Combat-related wounds are managed with wide débridement, irrigation, and delayed closure, per military doctrine.15 Initial treatment most frequently occurs in the theater of combat operations, where only basic resources are available. Following initial treatment, patients subsequently require aeromedical evacuation to a higher level facility outside the combat area. Evacuation may not always occur in a timely fashion, prompting the need for a method to safely allow delay of definitive management of combat-related wounds.

NPWT has been adopted as a useful tool for wound management in the setting of combat-related wounds. Early anecdotal reports of in-flight vacuum failure, which can lead to secondary wound complications, raised concern about the use of NPWT during aeromedical evacuation.14,26 In 2006, a commercially available NPWT system obtained Joint Airworthiness Certification status by the US military.26 Subsequently, Pollack et al26 assessed the safety of NPWT used during aeromedical evacuation of 218 US military members from the theater of combat operations in Iraq and Afghanistan to Landstuhl Regional Medical Center (LRMC) in Germany. Following initial débridement and irrigation of soft-tissue injuries and skeletal stabilization, patients underwent standard NPWT and were then evacuated to LRMC for additional wound care. Failure of the NPWT system was identified in 4.5% of patients. System failures included inadequate generation of a vacuum due to leaks in the dressing, thrombus obstruction of the tubing, and high volume output. Major complications occurred in only two patients; they arrived at LRMC with fever and a septic wound, which resolved after surgical débridement. Fang et al14 evaluated safety and feasibility of NPWT during aeromedical evacuation.
evacuation from LRMC to the continental United States. All patients arrived at destination facilities with functional NPWT systems; no in-flight complications were reported, and effects on flight crew workload were deemed negligible.

**Incisions at Risk of Breakdown**

The use of NPWT for management of closed surgical wounds with early signs of inadequate healing or those located at anatomic sites associated with high complication rates has not yet been fully explored. Although there is no direct contact between the wound bed and the open-pore foam, negative pressure at the incision site provides continuous evacuation of excessive drainage, thereby avoiding skin irritation and bacterial colonization while reducing edema. Some authors advocate the use of polyvinyl alcohol sponges with a pressure setting of −50 mm Hg; however, others recommend the use of polyurethane ether sponges with a pressure of −125 mm Hg.15,21

Stannard et al15 evaluated the use of NPWT for management of persistent wound drainage. The authors randomized 44 patients with persistent drainage lasting at least 5 days to either NPWT or treatment with a compressive dressing. The period of drainage was significantly shorter in the NPWT group than in the pressure dressing group (1.6 versus 3.1 days, respectively; P = 0.03). In addition, the rate of infection in the NPWT group was half of that in the pressure dressing group (8% versus 16%, respectively). The authors randomized an additional 44 patients with postoperative wounds following management of high-risk fractures (fractures of the calcaneus, tibial plateau, tibial pilon) to either NPWT or standard postoperative dressing. Wounds managed with NPWT required significantly less time to achieve grade 3 status, which was defined as drainage ≤2 quarter-size drops (1.8 versus 4.8 days, respectively; P = 0.02). However, similar rates of infection and wound breakdown were observed in both groups.15

**Skin Graft**

Several studies have reported improvement in skin graft incorporation with the use of NPWT, with pressure ranging from −50 to −80 mm Hg.2,21,12 Bolstering of the graft to the wound is more reliable with NPWT than with conventional methods, thereby increasing the rate of graft intake. Llanos et al20 studied 60 patients with wounds with skin loss treated with partial-thickness skin graft (PTSG) followed by either NPWT or standard bolstering. In the NPWT group, medial loss of PTSG was zero compared with 4.5 cm in the control group. Similar results have been consistently demonstrated in other studies.2,28,29

**Bacteria-specific Effect**

Bacterial wound colonization is considered a key factor in wound healing and infection. Clearance of bacterial clearance from the wound environment is a frequently cited benefit of NPWT. Although some studies have shown a significant decrease in the bacterial load of *Staphylococcus aureus* and *S. epidermidis* with the use of NPWT,2 others have found no difference in bacterial clearance with this modality, but rather an overall increase in bacterial load.30 Lalliss et al21 used an animal open fracture model to determine whether NPWT exerted a differential effect based on the type of colonizing bacteria. Following serial débridements every 48 hours for 6 days, NPWT proved more effective than WTD dressings for clearance of *Pseudomonas aeruginosa*. However, no significant difference was found for clearance of *S. aureus*. Mouès et al11 reported similar findings in a randomized study of 54 patients with full-thickness wounds who were treated with either NPWT or conventional WTD dressings. The authors noted a significant reduction in nonfermentative gram-negative rods in the NPWT group, whereas no difference was found in the WTD group. However, wounds treated with NPWT exhibited a substantial increase in *S. aureus*, compared with the WTD group, in which no increase in *S. aureus* bacterial load was found.

**Complications**

Failure of the VAC system to maintain a vacuum may pose a risk of wound infection.32,33 Loss of seal due to a puncture of the occlusive dressing, power loss during use of the motorized suction unit, and clogging of the drainage system (sponge and tubing) can potentially cause loss of effective suction. Therefore, it is important to use a system that allows adequate monitoring of suction.

Since 2007, 12 deaths have been related to the use of NPWT.34 The most frequent serious adverse event reported was bleeding, which occurred in most deaths associated with the use of NPWT. Extensive bleeding occurred when NPWT was used in patients with wounds near the groin or presternal region and when NPWT was used over vascular grafts.34 Patients taking anticoagulants and those in whom significant adhesion is found between the wound bed and dressing at the time of dressing removal have an increased risk of bleeding.34,35 This risk can be decreased by avoiding early
use of NPWT following vascular ligation in wounds adjacent to large vessels or in patients with coagulopathy. Bleeding from a delayed dressing change can be minimized by placing a nonadherent dressing or polyvinyl alcohol sponges in the base of the wound. Contraindications and patient factors to consider before NPWT placement are summarized in Tables 2 and 3.34

To prevent loss of suction, adequate dressing placement is crucial. After application of an alcohol-based skin preparation, the skin must be dry to allow adequate sealing of the adhesive dressing for generation of suction. Continuous monitoring of suction and NPWT systems with an alarm can facilitate early detection of seal loss.

### Cost

Reusable units typically used in the United States are not for sale and must be rented from the manufacturer by the day or the month (Table 1). Cost for use per day is based on contracts with both insurance providers and treatment facilities. At our institution, daily cost ranges from $70 to $130. This cost does not include dressing supplies ($40 to $140 per dressing) or replacement canisters ($35 to $84). In addition, special dressings (eg, silver-impregnated dressing) can increase the cost an additional 40% per dressing. Single-use, disposable NPWT systems can be purchased and typically cost between $500 and $600.

To date, formal studies on the cost-effectiveness of NPWT have not been performed. Studies that have marginally included this issue for analysis have suggested that the costs are similar to those associated with WTD but are less expensive than early free tissue transfer for the management of traumatic soft-tissue injuries.5

### Evidence-based Recommendations

Recently, evidence-based recommendations were established for the use of NPWT.34 Based on the quality of the available evidence, a scaling method was used to classify evidence to support that NPWT “must” (grade A), “should” (grade B) or “may” (grade C) be used in certain clinical scenarios. A grade D recommendation indicated that only a possible benefit could exist with use of NPWT. Notably, recommendations regarding the use of NPWT for acute management of traumatic soft-tissue injuries received only a grade C. The use of NPWT as a bridging therapy between several débridements received grade B recommendation. Grade A recommendations could be established only for management of skin grafting procedures.

### Future Advances

Based on the efficacy of ABPs for management of traumatic wounds, combination therapy consisting of NPWT and antibiotic infusion or use of antibiotic-laden cement is being evaluated as a potential solution to the issue of secondary S aureus colonization.2,16,37,39 In a study of 27 patients with infected surgical wounds, intermittent infusion of either antibiotics (eg, neomycin, bacitracin) or antiseptic solution (eg, polyhexanide) and NPWT yielded a healing rate of 96%.14 Another study compared the rate of recurrence of infection in patients treated with antibiotic cement beads alone and those treated with NPWT with antibiotic instillation.7 The authors
found that NPWT with antibiotic instillation was associated with a lower rate of recurrence than placement of antibiotic cement beads alone (10% versus 58%, respectively). However, other studies have reported that NPWT may reduce the effectiveness of antibiotic beads against *S. aureus*.37,38 One promising adjuvant is silver; in a recent animal study, commercially available silver-impregnated dressings used in conjunction with NPWT substantially reduced bacterial rebound.39,40

Based on the available data regarding combination therapy for management of wounds associated with orthopaedic trauma, one of the authors (D.J.S.) has proposed the concept of a ladder of bacteria reduction, which can be used to stratify management of wounds associated with orthopaedic trauma in the setting or suspicion of infection17 (Figure 5). NPWT is at the lowest rung of the ladder and corresponds to the lowest rate of bacterial clearance from a contaminated wound. ABP is at the highest rung and correlates with the highest rate of bacterial clearance.17 Two rungs of the ladder are assigned to adjuvant therapies: NPWT used with silver, which is located near the middle of the ladder, and NPWT used with ABP, which is closer to the top of the ladder.

**Summary**

NPWT is an alternative option for management of wounds associated with orthopaedic trauma. Benefits of this modality include the need for less frequent dressing changes and the reduction of pain. However, the available data do not conclusively support the use of NPWT to prevent infection, avoid free tissue transfer, or safely prolong time to definitive soft-tissue coverage.41 In addition, no definitive benefits have been reported for the use of NPWT for management of incisions at risk of breakdown or infection. Only in the setting of PTSG has NPWT consistently shown higher success rates than conventional wound management methods. Additional research, including cost analysis, is required to elucidate the clinical indications for NPWT and to determine the effectiveness of adjuvant therapies used in conjunction with NPWT.

**References**

Evidence-based Medicine: Levels of evidence are described in the table of contents. In this article, references 11, 25, 27, and 28 are level II studies. References 7, 24, and 38 are level III studies. References 1, 2, 8, 12-16, 18, 23, 26, 29, 32, and 33 are level IV studies.

References printed in **bold type** are those published within the past 5 years.

Use of Negative-pressure Wound Therapy in Orthopaedic Trauma


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