NEGATIVE PRESSURE WOUND THERAPY WITH INSTILLATION

Review of Evidence and Recommendations

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Negative Pressure Wound Therapy with Instillation: Review of Evidence and Recommendations

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Abstract

Negative pressure wound therapy with instillation (NPWTi) and dwell time is an adjunctive treatment modality for selected complex wounds. Because of the greater amount of research now available, a multidisciplinary expert panel comprising the fields of podiatry, plastic and general surgery, burn treatment, infectious diseases, and orthopedics was convened on July 11, 2015, to produce a summary of the data and recommendations on the use of NPWTi. The panel members each reviewed available published literature on NPWTi in the PubMed, Cochrane, and Google Scholar databases from 1 January 2012 up until 20 July 2015 using the string search term negative pressure wound therapy instillation provided by the panel moderator; there were no restrictions on the language or type of publication. Panel members discussed their experiences and worked to reach consensus on several predefined topics. NPWTi was found to be most appropriate for properly selected complex hosts or wounds such as patients with multiple comorbidities, patients with an American Society of Anesthesiology Classification ≥ 2, severe traumatic wounds, diabetic foot infections, and wounds complicated by invasive infection or extensive biofilm. NPWTi should not be used routinely to treat simple wounds or hosts without comorbidities. There is evidence that when NPWTi is added to standard of care in properly selected cases it provides better overall clinical outcomes than standard of care alone, even when including NPWT. Based on published evidence and panel member experience, the Panel recommends a dwell time – fluid briefly instilled into the wound and allowed to diffuse for a user-specified time – of 10-20 minutes followed by 2-4 hours of negative pressure at -125 mmHg, although larger wounds may need times of up to 6 hours. Normal saline (0.9%) is the preferred solution for NPWTi, except in special situations. NPWTi with dwell time is an adjunct to other standard principles of appropriate wound assessment and treatment (e.g., debridement, pressure offloading, systemic antibiotic therapy, vascular assessment and revascularization when needed, or glycemic control).

Introduction

Negative pressure has been employed historically for routine wound care, but its use in the form of a controllable device, combined with an interface material to uniformly spread a partial vacuum over a wound with resultant tissue microdeformation is a more recent development. Based on preliminary research conducted in the 1980s, Argenta and Morykwas conducted the first large investigation (N=300) of negative pressure wound therapy (NPWT) using the vacuum-assisted closure system (V.A.C.® Therapy, KCI, an Acelity Company, San Antonio, TX) that demonstrated it could promote granulation in acute, subacute, and chronic wounds. Although the technology has been improved substantially since that time, NPWT (V.A.C.® Therapy) is still comprised of a porous, foam interface that is placed into the wound and a semi-occlusive dressing that overlays the interface and seals the wound. This permits subatmospheric pressure to be transmitted to the wound from a vacuum source via a tube that is inserted through the semi-occlusive dressing on top of the interface. A canister is used to collect wound fluids. Today, several variations of NPWT are used in acute care, long-term care, and home settings for a variety of other clinical applications, such as over open fractures, deep soft tissue defects, mesh-graft fixation, and dehisced wounds.

The concept of cleansing a wound with fluid after debridement is at least 100 years old and is based on the work of Alexis Carrel during World War I. Carrel devised techniques for delivering Dakin’s solution directly into wounds. The technical basis for an updated instillation method occurred in 1996. The first publication on the subject was in 1998 and described positioning polyvinyl alcohol sponges with drainage tubes over the internal or external surfaces of acute or chronic wounds and
hermetically sealing them with a transparent film. Antibiotic or antiseptic solutions from gravity-fed bottles were instilled for 30 minutes followed by applying a partial vacuum of 20–80 kPa (150–600 mm Hg) applied for 3 hours; this cycle was repeated over the course of a week.\(^4\)\(^5\)

More recently, several studies have investigated differences between wound cleansing with saline, tap water, or no cleansers.\(^6\)\(^7\) In the 2012 Fernandez et al. meta-analysis, randomized controlled trials assessed the differences in wound healing and infection rates between wound cleansing using tap water, saline or no wound cleansing.\(^6\) No differences existed in infection rates or healing rates among groups that received tap water, saline, or no cleansing. Angeras and colleagues reported that cleansing with warm tap water significantly lowered the rate of wound infection when compared with cleansing using saline (5.4% vs. 10.3%, \(p<0.05\)).\(^7\) It is possible that surface cleansing of infected wounds may not remove enough debris or infectious materials to create a sufficient wound healing environment, resulting in no differences in the wound healing rates seen above. The evolution of wound cleansing to include a user-specified instillation soak time for the solution to penetrate the wounds, followed by fluid and wound debris removal using vacuum pressure, may offer whole wound cleansing to help promote a healing environment.

In 2002, KCI first marketed negative pressure wound therapy with instillation and dwell time (NPWTi; the V.A.C. Instill\(^\text{®}\) Wound Therapy, KCI, an Acelity company, San Antonio, TX), which introduced a second tube (in addition to the one for drainage) for the purpose of intermittently instilling solutions into the wound. Fluid was instilled via gravity into the foam interface from an intravenous bag or bottle. The solution was held (dwell time) at the wound site for a short period of time followed by removal of wound fluid under negative pressure; this sequence of events was repeated in cycles. Wolvos\(^8\) first reported on outcomes using this device in 2004, providing details on 5 patients in whose wounds a variety of topical solutions (e.g., lidocaine) were instilled, followed by a dwell time of 5 minutes, and negative pressure for 3 hours at -125 mmHg.

Figure 1. (A). A patient with an infected wound status post Achilles tendon rupture repair. Note the necrotic and infected deep tissue.
A more technologically sophisticated version of the V.A.C.® Wound Therapy device was introduced in 2011. This integrated system, known as the V.A.C. Ultra™ Therapy System with V.A.C. VeraFlo™ Instillation Therapy (KCI, an Acelity company, San Antonio, TX) is composed of the governing device, a volumetric pump and a VeraFlo™ Dressing. It is indicated for wounds that would benefit from application and removal of topical solutions and can be used as a management tool for a wide variety of wounds, including those with infections. The device delivers wound cleansers, antiseptics, and disinfectants to the wound followed by removal of fluid, wound debris, and infectious materials during the negative pressure step. No FDA approved topical wound solutions to treat infection exist; thus the V.A.C. Ultra™ Therapy with V.A.C. VeraFlo™ Instillation Therapy is not indicated for treatment of infection, for the prevention and treatment of biofilm, or for the delivery of nontopical antibiotics or drugs. It is currently intended for use in acute care hospital settings and often is used in the subacute setting (e.g., long-term acute care hospitals.) Features of the system include tools to allow the clinician to visually determine the correct instillation volume, perform a test cycle, and have the option of soaking the dressing with an instillation solution before dressing removal. There are two options for delivering solutions to the wound: the V.A.C. VeraT.R.A.C.™ pad (KCI, an Acelity Company, San Antonio, TX), which uses a single pad for both delivery of instillation solution and negative pressure, and the V.A.C. VeraT.R.A.C. Duo™ Tube Set (KCI, an Acelity Company, San Antonio, TX) which provides separate instillation and negative pressure pads for application at different dressing locations. The V.A.C. VeraFlo™ Dressing Kits (VeraFlo™ Dressing and VeraFlo Cleanse™ Dressing) (KCI, an Acelity Company, San Antonio, TX) include polyurethane ester foam dressings that are less hydrophobic than the traditional V.A.C.® GranuFoam™ Dressing (KCI, an Acelity Company, San Antonio, TX) and a drape with better moisture-resistant properties. A bench study indicates the VeraFlo™ Dressing

Figure 1. (B). After surgical debridement and 3 days of NPWTi with polyhexamethylene biguanide (PHMB). Note the improved quality of tissue and a robust granulation tissue response.
may have enhanced fluid distribution properties compared to the conventional V.A.C.® GranuFoam™ Dressing, a desirable property for instillation therapy. A comparative, noninfected porcine wound model study indicated after 7 days of therapy, V.A.C. VeraFlo™ Therapy with saline instillation was associated with increased granulation of the wound compared to V.A.C.® Therapy alone. Although these results have not been confirmed in human studies, Figure 1A shows a patient with an infected, dehisced wound following an Achilles tendon rupture repair in which there is necrotic, infected deep tissue. Figure 1B demonstrates the improved quality of tissue and a robust granulation tissue response following surgical debridement and 3 days of NPWTi with Prontosan® Wound Irrigation Solution (B. Braun, Bethlehem, PA).

There is a difference between NPWT with continuous irrigation and NPWTi with dwell time after instillation (NPWTi-d). Continuous irrigation of a solution, while simultaneously applying a partial vacuum, is possible with some devices, such as the Sved™ Wound Treatment System (Cardinal Health Inc., Dublin, OH). Several case studies of this variation have been published. NPWTi-d differs by having the fluid briefly instilled into the wound, followed by a dwell time, which has been shown in bench studies to facilitate exposure of the wound bed – including tunnels and undermining – to the solution.

In 2013, a group of physicians in the field of negative pressure and antiseptics published international consensus guidelines designed to address the appropriate use of NPWTi. Since these were formulated, additional outcomes-based data on this therapy have been published. These data, combined with an increasing depth of experience by frequent users of this medical device, suggested it was time for an update on this adjunctive wound therapy.

Methods
Panel Meeting
A multidisciplinary panel of physicians with extensive experience in NPWTi and antiseptics from the fields of podiatry, plastic and general surgery, burn treatment, infectious diseases, and orthopedics was convened on July 11, 2015, in Dallas, TX. They were tasked with review of the available literature on NPWTi – provided to panel members by sponsors – and asked to deliberate on several predefined topics before finally discussing their personal experiences with the technology. The topics selected for discussion included the definitions used in the literature, the efficacy and effectiveness of NPWTi, the appropriate uses of NPWTi, optimal therapy parameters of NPWTi, potential topical wound solutions that could be used, perceived barriers to using the system and how these might be resolved, and potential areas for future exploration. Each panel member presented his research and clinical experience on NPWTi, as delivered by V.A.C. VeraFlo™ Therapy, as well as summaries of research on pre-assigned topics, which was followed by a roundtable discussion for each topic, guided by a moderator.

Literature Search
A literature search was designed to identify clinical studies that involved the use of NPWTi. The search used the string “negative pressure wound therapy instillation” in the Pubmed, Cochrane, and Google Scholar databases, seeking publications from 1 January 2012 up until 20 July 2015; there were no restrictions on the language or type of publication. As a cross-check, the panel moderator searched Pubmed using the algorithms listed by Back et al., with the addition of the term instillation to ensure the search was sufficiently complete for an update of the studies located by these authors (i.e., from the beginning of 2012); the same filters were used, but with no language restriction. All abstracts were reviewed by panel members for relevance and for those meeting our criteria (see Level of Evidence section). Full text of the article, letters to the editor, and other cited documents were provided to panel members if they contained comments on relevant clinical studies.

Level of Evidence
With regard to clinical outcomes only, the level of
Table 1. Clinical, biochemical or microbiological outcomes of human clinical studies

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Study Population</th>
<th>Study Description</th>
<th>Sample Size</th>
<th>Outcomes</th>
<th>Evidence Level</th>
<th>Strengths &amp; Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fleischmann et al.</td>
<td>1998</td>
<td>Acute infections, chronic osteomyelitis or chronic wounds</td>
<td>NPWTi case series; Non-commer- cial system; solution: antiseptic or antibiotic; dwell: 30 min; NP: 3 h, 150-600 mmHg, 1 week treatment</td>
<td>27</td>
<td>Immediate/delayed wound closure: 81%; skin grafting: 11%; healing: 7%; follow-up (3-14 mos): 1 recur- rence osteomyelitis</td>
<td>IV</td>
<td>Variety of wounds and solutions; uniform treatment time; all outcomes satisfactory in short- and long-term; non-comparative</td>
</tr>
<tr>
<td>Wollost (2004)</td>
<td>BK3, TMA, 5th ray/ hallux amputation, infection of breast incision, harvest site for CABG</td>
<td>NPWTi case series; V.A.C. Instill; solution: LC; vancomycin (≤ LC), gentamicin (≤ LC), tobramycin (≤ LC); instill: 15-60 sec; dwell: 5 min; NP: 3 h, 125 mmHg, 5-24 days treatment</td>
<td>5</td>
<td>Less pain and complete skin graft take (1); healing (4)</td>
<td>IV</td>
<td>Variety of wounds and solutions; uniform treatment protocol; good short- term outcomes but lack of long-term outcomes; non-comparative; small sample size</td>
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<tr>
<td>Bernstein &amp; Tam (2005)</td>
<td></td>
<td>NPWTi case series; V.A.C. Instill; solution: polymyxin B/bacitracin; dwell: 5 min; NP: 6 h, 125 mmHg, 2-9 days treatment</td>
<td>5</td>
<td>Healed (4), healing (1)</td>
<td>IV</td>
<td>Fairly uniform treatment protocol; variable-term outcomes but all satisfactory; non-comparative; small sample size</td>
<td></td>
</tr>
<tr>
<td>Kir et al. (2006)</td>
<td></td>
<td>NPWTi case series; V.A.C. Instill; solution: bacitracin/neomycin; instill: 12-18 sec; dwell: 10-20 min; NP: 60 min; pressure: NR, ~15 days treatment</td>
<td>5</td>
<td>Infection resolved in all patients</td>
<td>IV</td>
<td>Hardware not removed while NPWTi was instituted; satisfactory outcomes; unknown suction pressure; non-comparative; small sample size</td>
<td></td>
</tr>
<tr>
<td>Gabriel et al. (2008)</td>
<td>Complex infected wounds</td>
<td>Prospective cohort-historical control design: C: standard of care (debridement, moist wound care, antibiotics), I: NPWTi + antibiotics</td>
<td>30 C: 15 I: 15</td>
<td>Mean days of treatment: C: 36.5, I: 9.9, p&lt;0.001; Mean days to infection resolution: C: 25.9, I: 6.0, p&lt;0.001; Mean days to wound closure (various methods): C: 29.6, I: 13.2, p&lt;0.001; Mean days to patient discharge: C: 39.2, I: 14.7, p&lt;0.001</td>
<td>II</td>
<td>Outcomes significantly better for NPWTi vs. control group; could have been some bias in selecting control group members; small sample size</td>
<td></td>
</tr>
<tr>
<td>Timmers et al. (2009)</td>
<td>Post-traumatic osteomyelitis, mainly pelvis or leg (I: 93%; C: 98%)</td>
<td>Prospective cohort-historical control design: C: standard of care (debridement, implantation of gentamicin polymethyl-meth- acrylate beads, long-term IV anti- biotics), I: NPWTi + debridement/ antibiotics</td>
<td>124 C: 94 I: 30</td>
<td>recurrence osteomyelitis (%): 58.5 (C), 10 (I), p&lt;0.0001; Cumulative hospital stay (median, days): C: 73, I: 36, p&lt;0.0001</td>
<td>II</td>
<td>Outcomes significantly better for NPWTi vs. control group; long-term follow-up good; considerable bias in control group selection and disparity in sample sizes</td>
<td></td>
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<tr>
<td>Leffler et al. (2009)</td>
<td>Subacute/chronic osteomyelitis (LE, upper extremity)</td>
<td>NPWTi case series; V.A.C. Instill; solution: polyhexanide; mean instill time: 20 sec; dwell time: 20 min, NP: 3-6 h; pressure and days of treatment: NR</td>
<td>6</td>
<td>Bacterial swabs/tissue biopsies sterile after NPWTi; after 3-10 mos, no osteomyelitis recurrence</td>
<td>IV</td>
<td>Satisfactory outcomes; missing some NPWTi treatment data; missing long- term follow-up; non-comparative; small sample size</td>
<td></td>
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<tr>
<td>Schinitter et al. (2009)</td>
<td>Infected wounds, bone, sepsis sites</td>
<td>Radical debridement with NPWTi case series; V.A.C. Instill; solution: polyhexanide; instill time: 10-30 sec; dwell time: 10-15 min; NP: 300-600 mmHg, 6-60 days treatment</td>
<td>15</td>
<td>All infection resolved and complete wound healing achieved</td>
<td>IV</td>
<td>Satisfactory outcomes; missing some NPWTi treatment data; missing long- term follow-up; non-comparative; small sample size</td>
<td></td>
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<tr>
<td>Köster (2009)</td>
<td>Knee endoprosthetic infections</td>
<td>NPWTi case series; V.A.C. Instill; solution: polyhexanide; instill time: 10-30 sec; dwell time: 10-15 min; NP: 45-60 min; pressure: NR; days of treatment: 4-18</td>
<td>10</td>
<td>Infection resolved in all cases, but 1 case had a re-infection (10%)</td>
<td>IV</td>
<td>Mostly satisfactory outcomes and long- term follow-up; missing some NPWTi treatment data; non-comparative; small sample size</td>
<td></td>
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<tr>
<td>Lehner et al. (2009)</td>
<td>Periprosthetic infection from hip arthroplasty; early infection: 19, late infection: 4</td>
<td>NPWTi case series; V.A.C. Instill; solution: polyhexanide; instill time: up to 40 sec; dwell time: 15 min; NP: 60 min; pressure: 125 mmHg; days of treatment: NR</td>
<td>23</td>
<td>Success rate (no endoprosthes- is explantation): 84% (early infec- tion), 50% (late infection)</td>
<td>IV</td>
<td>Mostly satisfactory outcomes and long- term follow-up; missing some NPWTi treatment data; non-comparative; relatively small sample size</td>
<td></td>
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<tr>
<td>Raed et al. (2010)</td>
<td>Large VLUs with high bioburden</td>
<td>NPWTi case series; V.A.C. Instill; solution: Dakin’s Solution; instill time: NR; dwell time: 10 min; NP: 60 min; pressure: NR; days of treatment: 10</td>
<td>5</td>
<td>All infection resolved, 100% take with STSG, and complete wound healing remained at 2 years</td>
<td>IV</td>
<td>Satisfactory outcomes and long-term follow-up; missing key NPWTi treat- ment data; non-comparative; small sample size</td>
<td></td>
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<tr>
<td>Rashid et al. (2010)</td>
<td>Chronic osteomyelitis</td>
<td>NPWTi case series; V.A.C. Instill; solution: NR; dwell: NR; NP: NR; days of treatment: NR</td>
<td>10</td>
<td>Mean hospital stay: 33 days 2/10: treatment failures</td>
<td>IV</td>
<td>Research letter; Satisfactory out- comes; missing all NPWTi treatment data; missing long-term follow-up; non-comparative; small sample size</td>
<td></td>
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</tbody>
</table>
Lehner et al. (2011) Infected orthopedic implants (THA 62.5%, TKA 31.3%, 6.2% osteosynthetic material) NPWTi case series; V.A.C. Instill; solution: polyhexanide (96.9%) saline (3.1%); dwell: 5-30 min; pressure: 125-200 mmHg; days of treatment: 9-46 32 Implant retention rate: 86% (acutely infected), 80% (chronically infected) IV Mostly satisfactory outcomes but short-term follow-up; considerable variation in NPWTi protocol; non-comparative

Flueraru et al. (2013) Infected wounds that failed to respond to NPWT or complex wounds (e.g., large undermining tracts or deep wounds) NPWTi case series; V.A.C. Instill; solution: normal saline; dwell: 10 min; NP: 4-12 h; pressure: 125 mmHg; mean days of treatment: 12.2 24 Previously treated with NPWT: granulation followed by surgical closure; complex wounds: results for 11/12 considered successful IV Uniform NPWTi protocol and satisfactory outcomes but follow-up time and "success" not defined; non-comparative; small sample size

Brinkert et al. (2013) Variety of infected wounds or at high risk of infection (e.g., open fractures, infected hematomas, PUs, non-healing postoperative dehiscence wounds) NPWTi case series; V.A.C. VeralFlo; solution: normal saline; dwell: 10 min; NP: 60 min; pressure: 125 mmHg; days of treatment: 7-54 131 98% of wounds could be closed by skin graft, flap, or primary suture with no incidence of wound recurrence or dehiscence IV Large sample size, uniform NPWTi protocol and satisfactory outcomes but follow-up time and "success" not defined; time to surgical closure or wound healing not reported; non-comparative

Wolvos et al. (2013) Variety of infected or complex wounds NPWTi case series; V.A.C. VeraFlo; solution: Microcyn (5), Dakin’s (1); dwell: 5-10 min; NP: 2-4 h; pressure: 100-125 mmHg; days of treatment: 7-54 6 Successful transition out of acute care or wound healed IV Satisfactory outcomes but follow-up time and "success" not defined; non-comparative; small sample size

Schreiner et al. (2013) Variety of infected or complex wounds NPWTi case series; V.A.C. Instill; solution: polyhexanide; mean dwell: 18 min; NP: 2 h; pressure: 75-150 mmHg; mean days of treatment: 6.5 11 10/11 patients achieved sterile wound status prior to secondary wound closure; no wound recurrence in all wounds IV Satisfactory outcomes but follow-up time and "success" not defined; non-comparative; small sample size

Goss et al. (2014) DFUs, VSPUs, and other wound etiologies with significant bacterial bioburden (>10^4 CFU/g tissue) NPWT (C) vs. NPWTi (I); Prospective contemporary cohort design I: V.A.C. VeraFlo; solution: Dakin’s; dwell: 10 min; NP: 60 min; pressure: 125 mmHg; days of treatment: 7 C: NP: 125 mmHg, 7 days of treatment 13 patients, 16 wounds; Wounds: C: 8 I: 8 Mean absolute reduction in bacterial count (CFU/g tissue) after 1 week: C: 10^9 x 10^9; C: 28.7 x 10^10, (p=0.016) At end of therapy no significant difference between I and C groups (p=0.44); C group had 16% increase in bacteria vs. 87% reduction for I group (p=0.078) II Outcomes better for NPWTi vs. control group but significance depended on outcome and test; very small sample size and study not sufficiently powered to show outcome differences

Kim et al. (2014) Ischemic, neuropathic, surgical, traumatic, and other wounds, PUs, VLUs NPWT (C) vs. NPWTi (I) (2 subgroups I, and IJ); retrospective cohort-historical control design C: InfoV.A.C.; NP: -125 mm Hg; 7 days of treatment; I: V.A.C. VeraFlo; solution: polyhexanide + betaine; dwell: 6 min; NP: 3.5 h; pressure: -125 mmHg; days of treatment; 7 I: V.A.C. VeraFlo; solution: polyhexanide + betaine; dwell: 20 min; NP: 2 h; pressure: -125 mmHg; days of treatment: 7 142 C: 74 I: 34 C: 34 I: 34 Analysis*: Mean number of OR visits: C: 3.0, I: 2.4, I: 2.6, p=0.04, 0.003; Mean length of hospital stay (days): C: 14.9, I: 19.8, I: 11.4, p=0.10 (NSS), p=0.03; Mean time to final surgical procedure (days): C: 9.23, I: 7.8, I: 7.5, p=0.04, p=0.002; Percentage of wounds closed by discharge (%): C: 62, I: 94, I: 80, p=0.0004, p=0.08 (NSS); Wound culture improvement (exclude gram-negative, Corynebacterium, yeast; %): C: 63, I: 90, I: 65, p=0.0001, p=0.77 (NSS). III Outcomes always better for NPWTi vs. control group but I group had better and more statistically significant results than I group compared to control group; groups well matched in terms of patient and wound parameters; sample sizes reasonable; clear study eligibility

Gabriel et al. (2014) Infected or critically colonized wounds from LE, upper extremity, and trunk NPWT (C) vs. NPWTi (I); Retrospective cohort design C: V.A.C. Therapy; NP: -125 mmHg; mean days of treatment: 20.9 I: V.A.C. VeraFlo; solution: saline or polyhexanide; dwell: 1-60 sec; NP: 1-2 h; pressure: 125 mmHg; mean days of treatment: 4.1 82 C: 34 I: 48 Mean hospital stay (days): C: 27.4, I: 8.1, p<0.0001 Mean time to wound closure (days): C: 20.9, I: 4.1, p<0.0001 Mean number of surgical debridements (OR): C: 4.4, I: 2.0, p<0.0001 III Outcomes always and significantly better for NPWTi vs. control group; sample sizes reasonable; cohorts well matched temporally but some bias in how well groups of matched due to non-reported patient/wound parameters; considerable variability in NPWT parameters but results still robust

Yang et al. (2015) VLUs with area >100 cm^2 NPWTi case series; V.A.C. (type: NR); solution: Dakin’s; dwell: 10 min; NP: 1 h; pressure: NR; days of treatment: 7 10 ulcers in 7 patients Mean length of hospital stay: 13.4 days STSG take at 30 days (%): 91 IV Satisfactory outcomes but follow-up time variable and "success" not defined; non-comparative; small sample size

Szklavari et al. (2015) Empyema thoracis (primary, post-op, or recurrent pleural empyema) NPWTi case series; V.A.C. Instill; solution: polyhexanide; dwell: 20 min; NP: 3 h 40 min; pressure: 125 mmHg; days of treatment: 5-25. 15 Thoracic sterilization: 13/15 patients Healed: 13/15 patients IV Satisfactory outcomes but follow-up time variable and "success" not defined; non-comparative; small sample size

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*Analysis*: Mean number of OR visits: C: 3.0, I: 2.4, I: 2.6, p=0.04, 0.003; Mean length of hospital stay (days): C: 14.9, I: 19.8, I: 11.4, p=0.10 (NSS), p=0.03; Mean time to final surgical procedure (days): C: 9.23, I: 7.8, I: 7.5, p=0.04, p=0.002; Percentage of wounds closed by discharge (%): C: 62, I: 94, I: 80, p=0.0004, p=0.08 (NSS); Wound culture improvement (exclude gram-negative, Corynebacterium, yeast; %): C: 63, I: 90, I: 65, p=0.0001, p=0.77 (NSS).
evidence of individual NPWTi studies supporting the efficacy or effectiveness was defined as follows:14

I: high-quality, multicenter or single-center, randomized controlled trial with adequate power;

II: lesser-quality, randomized controlled trial; prospective cohort or comparative study;

III: retrospective cohort or comparative study; case-control study;

IV: case series with pre-post test or only post test;

V: expert opinion developed via consensus process; case report or clinical example.

Clinical studies were selected for analysis if they were level IV or above. A case series was defined as any study with 4 or more human subjects resulting in the reporting of any clinical, biochemical, or microbiological outcome.

Scope of NPWTi: Efficacy and Effectiveness

After reviewing the papers from our literature search, 23 studies reporting clinical outcomes were selected. Of these, 17 were non-randomized, non-blinded case series (level IV evidence), and 6 were comparative studies (level III [n=2] and II [n=4]) (see Table 1).17,18,30-32,35 The majority of the case series were relatively small studies except for the one conducted by Brinkert et al.,37 which enrolled 131 patients. Two of the comparative studies had a non-randomized, non-blinded prospective cohort versus historical control design,31 one was a non-randomized, non-blinded retrospective cohort study with historical controls,31 one was a prospective randomized, non-blinded cohort study,30 one was a non-randomized, non-blinded retrospective cohort study,32 and one was a randomized controlled trial (RCT).34 We noted that before 2008, antibiotic solutions were commonly used, but in the more recent studies, antiseptics have been more commonly used. Outcomes in most of these case series were poorly reported, including sometimes failing to state the duration of follow-up and not clearly defining

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al.16 (2015)</td>
<td>Infected wounds requiring surgical debridement in a hospital setting</td>
<td>NPWTi with normal saline (I) vs. NPWTi with polyhexanide + betaine (C), single site, non-blinded RCT. V.A.C. V: Alleviate; Fo: solution: normal saline (0.9%), I or polyhexanide + betaine (0.1%, C); dwell: 20 min; NP: 2 h; pressure: 125 mmHg; mean days of treatment: NR</td>
</tr>
<tr>
<td>100</td>
<td>Mean number of operations: I: 2.5, C: 2.6 (p=0.19, NSS) Length of stay (days): I: 13.6, C: 14.5 (p=0.68, NSS) Time to final surgical procedure (days): I: 5.7, C: 7.7 (p=0.04) Percentage of wounds closed/closed: I: 85.7, C: 92.2 (p=0.35, NSS)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Pragmatic design using surrogate outcomes; superiority rather than non-inferiority design; study lacked information regarding allocation concealment, sample size calculations, data imputation methods; no adjustment for confounding factors or multiplicity of statistical testing</td>
<td></td>
</tr>
</tbody>
</table>

BKA: below-the-knee amputation; C: control group; CABG: coronary artery bypass graft; CFU: colony forming unit; DFU: diabetic foot ulcer; ESRD: end-stage renal disease; h: hours; I: NPWTi group; IV: intravenous; LC: lidocaine; LE: lower extremity; min: minutes; mos: months; NP: negative pressure time; NR: not reported; NSS: not statistically significant; PU: pressure ulcer; PVD: peripheral vascular disease; RCT: randomized controlled trial; sec: second; STSG: split thickness skin graft; TKA: total knee arthroplasty; TMA: transmetatarsal amputation; VLU: venous leg ulcer; VSU: venous stasis ulcer; V.A.C.: V.A.C. (Vacuum Assisted Closure); V.A.C. VeraFlo: solution: normal saline (0.9%, C); dwell: 20 min; NP: 2 h; pressure: 125 mmHg; mean days of treatment: NR; vs: versus; W: wound.
clinical success. The non-randomized, non-blinded studies conducted by Brinkert et al.\textsuperscript{27} and Fluieraru et al.,\textsuperscript{26} which employed normal saline as the instillation solution, had outcomes similar to the case series that used antiseptic solutions.\textsuperscript{5,8,23,25,29,33,34}

The earliest comparative investigation was a non-randomized, non-blinded study in which 30 patients with complex, infected wounds were treated with moist wound dressings and standard wound care (surgical debridement and antibiotics, as needed) in the historical cohort control group or with standard wound care plus NPWTi in the prospective cohort.\textsuperscript{17} To be included in the study, the patient needed to have a complex trunk or extremity wound from which a swab culture grew $>10^5$ organisms. Additionally, the patient had to be over 40 years old, and had to have necrotic tissue in the wound. The patients in the retrospective control group were treated during a time period that considerably overlapped that of the intervention group, which likely helped to minimize selection bias. Successful treatment of infection was noted as absence of positive swab cultures following treatment. The groups were well matched on patient age, wound area, serum albumin level, smoking history, and diabetes. The intervention group received a uniform cycle NPWTi protocol consisting of 50–75 mL of silver nitrate instilled for 30–45 seconds followed with a 1-second hold time and 2 hours of negative pressure at -125 mmHg administered for 2–20 days. Several clinical outcomes were consistently and significantly better for the NPWTi group compared to the control group: infection was cleared nearly 4 times as fast (6.0 days versus 25.4 days, $p<0.001$); time to wound closure was less than half as long (13.2 days versus 29.6 days, $p<0.001$) (Table 1). Treatment time and time to discharge were also significantly shorter for patients treated with NPWTi compared to the controls. Limitations of this study, as judged by the Panel, included the relatively small number of patients, possible bias in the selection of control group, and the lack of adjustment for multiplicity of statistical testing.

In 2009, Timmers et al.\textsuperscript{18} investigated the use of NPWTi in patients with post-traumatic osteomyelitis of the pelvis or leg. Patients admitted over a 4-year period received extensive debridement, intravenous antibiotics, and an instilled solution of polyhexanide with a dwell time of 10–15 minutes, followed by 8–12 hours of negative pressure (-300 to -600 mmHg; these are not manufacturer-recommended settings) over a period of 6–60 days (Table 1). Outcomes in these patients were compared with a historical control group, constituted from admissions to two other departments at the same medical center during an earlier 20-year period. These control patients underwent surgical debridement, followed by implantation of gentamicin polymethylmethacrylate beads, and received long-term antibiotics. Control patients were matched to the intervention group by anatomic site and severity of osteomyelitis. The groups appeared to be well matched by patient age and presence of comorbidities, but there was a large disparity in sample sizes (NPWTi group: n=30; control group: n=94). After a follow-up time of 43–89 months, 10% of the NPWTi patients had recurrence of osteomyelitis, compared to 58.5% of the control patients ($p<0.0001$). By univariate analysis, no statistically significant difference was found between the two groups in the length of their first hospital stay, but because of more frequent recurrence of osteomyelitis in the control group, their median cumulative hospital stay was twice as long as for the intervention patients (73 days versus 36 days, $p<0.0001$). The number of surgical interventions was also significantly higher in the control group compared to the intervention group (5 versus 2, $p<0.0001$). Limitations of this study, as judged by the Panel, included a disparity in sample sizes between the groups and bias in the selection of control group as reported by the authors.

Goss et al.\textsuperscript{30} conducted a randomized, non-blinded prospective cohort study in which sequential patients seen over a year with chronic lower extremity wounds were assigned to 1 week of treatment with either NPWT or NPWTi to assess differences in bioburden after treatment. Patients in both groups underwent surgical debridement and had quantitative bacterial
culture of their wounds before and after treatment. All patients then received a split-thickness skin graft. The NPWT group (6 patients, 8 wounds) received continuous negative pressure of -125 mmHg while the NPWTi group (7 patients, 8 wounds) had Dakin’s solution (quarter strength) instilled with a dwell time of 10 minutes followed by the same negative pressure for 1 hour. The NPWT and NPWTi groups were similar at baseline, although there were substantial differences in predebridement wound area (123 cm² versus 63 cm²) and wound duration (23 months versus 30 months). On enrollment, both groups had bioburden >10⁶ and the 1-log reduction in wound bioburden following NPWTi was not statistically or clinically significant. There was a significantly higher bacterial count at baseline in the intervention group compared to the control group (3.7 vs. 1.8 x 10⁶ CFU/g tissue, p=0.016); after 1 week the difference in bacterial counts between the groups was not statistically significant (2.6 x 10⁵ vs. 2.8 x 10⁵). While the absolute reduction in bioburden between the groups was statistically significant (p=0.016), the control group had a 16% increase in bacteria versus an 87% reduction for the intervention group, and this was not statistically significant (p=0.078) (Table 1). Thus, this investigation suggested that NPWTi may have a greater impact on bacterial bioburden than NPWT under controlled conditions, but it was underpowered in respect of outcomes (sample size too small), nonrandomized, and the results were limited to the use of Dakin’s solution.

A non-randomized, non-blinded retrospective cohort-historical control study carried by Kim et al. enrolled patients with a variety of infected chronic wounds (mostly in the lower extremity) if they required hospital admission and at least two operative debridements, and if they were treated with NPWT (controls) or NPWTi (intervention group). All intervention subjects received an instillation of polyhexanide + betaine (Prontosan) in their wounds, but the group was further divided into those whose wounds had a dwell time of 6 minutes and negative pressure for 3.5 hours (I₁ group) and those with a dwell time of 20 minutes and negative pressure time of 2 hours (I₂ group). The negative pressure for all wounds in the study was -125 mmHg. At baseline, the patient parameters of the groups were similar, but the proportion of wounds located on the forefoot was higher in the I₁ group and lower for wounds located on the hindfoot or heel in both intervention (I₁ and I₂) groups (p=0.04 and p=0.03, respectively). The study found the mean number of OR visits was significantly lower for the intervention groups compared to the control group (control: 3.0; I₁: 2.4; I₂: 2.6; p=0.04, p=0.003; comparisons made between control and I₁ and control and I₂ groups; Table 1). The mean length of hospital stay was also shorter in the intervention groups compared to the control group, but was only statistically significant for the I₂ group (control: 14.9 days; I₁: 11.9 days; I₂: 11.4 days; p=0.03). However, the time to final surgical procedure was significantly shorter for both intervention groups when compared to the control group: (control 9.2 days; I₁: 7.8 days; I₂: 7.5 days; p=0.04, p=0.002). Interestingly, the percentage of wounds closed by the time of hospital discharge was only significantly different between the control and I groups (control: 62%; I₁: 94%; I₂: 80%; p=0.0004). Wound culture improvement, defined as the progression to no growth or a decrease in the qualitative bacterial amounts of cultured micro-organism, was slightly lower in the control group versus the I groups. However, when gram-negative bacteria, Corynebacterium spp, and yeast (organisms that are often nonpathogenic) were excluded, the difference between the control and I₁ groups was statistically significant (control: 63%; I₁: 90%; I₂: 65%; p=0.0001). This retrospective, albeit well-controlled, study suggests that when added to standard of care, NPWTi with Prontosan instillation was more beneficial than NPWT with respect to clinical outcomes. Limitations of the study included its retrospective nature, unconfirmed diagnosis, and selection bias; factors that might have influenced the results include duration of the negative pressure, volume of the instillation fluid, and the minimum or maximum duration of therapy.

A non-randomized, non-blinded retrospective cohort study by Gabriel et al. analyzed patients with infected or critically colonized wounds on the lower and upper extremities and trunk. The study showed clinically and
Negative Pressure Wound Therapy with Instillation

There were statistically significant differences between groups treated with NPWT or NPWTi, in addition to standard of care (debridement and systemically administered antibiotic therapy). The wounds in the NPWTi group (n=48) were instilled with normal saline or polyhexanide, with a dwell time of 1–60 seconds and a negative pressure time of 1–2 hours. The NPWT control group was selected from patients at the same medical facility over the same 3.4-year time frame. Patients were between ages 21-80 and each had an infected or critically colonized wound treated with NPWT (n=34). The mean patient age was similar in the two groups. The authors used a negative pressure of -125 mmHg for both groups, but the mean number of days of treatment was 4 times longer for the control group than the intervention group (20.9 days compared to 4.1 days) (Table 1). The mean hospital stay was more than 3 times shorter for the intervention group compared to the control group (8.1 days versus 27.4 days, \(p<0.0001\)) and mean number of operative debridements was less than half for the NPWTi group compared to the control group (2.0 versus 4.4, \(p<0.0001\)). Likewise, wounds in the intervention group had a much faster wound healing trajectory compared to wounds in the control group (4.1 days versus 20.9 days to heal, \(p<0.0001\)).

Limitations of this study included its retrospective design, potential selection and information bias, and missing data or variables, failure to match groups at baseline on risk factors for delayed healing, as well as the fact one might argue an antiseptic might be preferable in patients who have minimal formal debridement, in contrast to results seen by Kim,\(^{35}\) where aggressive serial debridement yielded good results when using saline alone.

Finally, a single-site, non-blinded RCT was conducted by Kim et al.\(^{35}\) in which patients with infected wounds requiring surgical debridement at a hospital (the majority neuropathic or surgical) were treated with NPWTi (dwell time 20 minutes and suction time of 2 hours) but randomized to different solutions: 0.9% normal saline or polyhexanide + betaine (Prontosan). Within 48 hours of admission, all infected wounds received sharp excisional debridement in the OR and then pulsatile irrigation (normal saline), followed by NPWTi, and oral or parenteral antibiotics. Further OR-based excisional debridement and NPWT dressing changes were performed every 2–4 days. The final operation (primary wound closure, local or free flap coverage, application of a xenograft or split thickness skin graft or debridement alone) was conducted based on surgeon judgment guided by qualitative culture analysis.

<table>
<thead>
<tr>
<th>Author(s)/Reference</th>
<th>Definition</th>
<th>Panel Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mustoe et al.(^{36})</td>
<td>Wounds that do not heal after 3 months of treatment</td>
<td>Definition may be too broad</td>
</tr>
<tr>
<td>Ferreira et al.(^{37})</td>
<td>(1) Wounds in the lower extremity of diabetic patients (2) Pressure ulcers (3) Chronic venous ulcers (4) Wounds following extensive necrotic processes caused by infections (Fournier’s and other) (5) Chronic wounds related to vasculitis and immunosuppressive therapy that have not healed using simple care.</td>
<td>(1) Depends on severity: many Wagner 1 and 2 DFUs can heal with good wound care alone (2) Stage III/IV PUs (3) Depends on bioburden, chronicity, inflammatory factors, etc.</td>
</tr>
<tr>
<td>Park et al.(^{38})</td>
<td>(1) Wounds involved with traumatic and orthopedic blunt or penetrating injuries, particularly in the extremities (2) Massive soft tissue infections including necrotizing fasciitis, gas gangrene and Fournier gangrene.</td>
<td>(1) Depends on nature of fracture/damage</td>
</tr>
<tr>
<td>Tricco et al.(^{39})</td>
<td>(1) Wounds resulting from chronic disease (e.g., venous insufficiency, diabetes) (2) Pressure ulcers (3) Nonhealing surgical wounds</td>
<td>(1) Depends on severity: many Wagner 1 and 2 DFUs can heal with good wound care alone; for VLUs on bioburden, chronicity, inflammatory factors, etc. (2) Stage III/IV PUs (3) Dehisced/infected wounds especially.</td>
</tr>
</tbody>
</table>

DFUs= diabetic foot ulcers; PUs= pressure ulcers; VLUs= venous leg ulcers.
tissue pathology, wound appearance, and serological infection biomarkers. Intent-to-treat analysis demonstrated no statistically significant differences between the groups in regard to number of operations, length of hospital stay, the percentage of wounds that were closed or covered during the study or follow-up at 1 month, although the mean time to the final surgical procedure was significantly lower for the normal saline–treated group compared to the polyhexanide + betaine–treated group (5.7 days versus 7.7 days, $p=0.04$). Although no formal non-inferiority analysis was undertaken, results suggest that in regard to type of instillation solution, normal saline may be as effective as Prontosan, although definitive conclusions cannot be drawn. Limitations of the study included use of surrogate endpoints, the aggressiveness of the serial debridement, lack of a control group, possible investigator bias, lack of blinding, and use of effectiveness rather than efficacy in the study design.

In summarizing the available literature, the evidence level of the available papers is relatively low with only one RCT published to date. There is a consistent trend suggesting that when adjunctive use of NPWTi is added to standard wound care it provides better clinical outcomes overall than just standard wound care, even when that standard includes NPWT.

### Appropriate Use of NPWTi

#### Panel Recommendation 1

NPWTi is appropriate for properly selected patients, including patients with substantial comorbidities that impair wound healing or response to infection or those who have a complex wound. NPWTi should not be used routinely to treat uncomplicated wounds or hosts without clinically significant comorbidities.

Two major factors that can help determine when NPWTi use is appropriate are the complexity of the wound and the host. There is no universal definition of a complex wound, but several classifications have been proposed (Table 2). In general, healing complex wounds requires more than the standard treatments, such as immediate or extensive surgery, or a requirement for other adjunctive treatments (e.g., revascularization). A complex host generally refers to a patient in whom the response to a pathogen or injury is either inappropriate (i.e., hypercytokinemia) or suboptimal, usually because of a compromised immune system.

The Panel proposed two situations that satisfy the idea of a complex wound or patient: 1) an American Society of Anesthesiologists physical status classification of $\geq 2$, or 2) two or more clinically relevant comorbidities, such as coronary artery disease, peripheral vascular disease, active cancer, renal failure or diabetes mellitus. Specific examples of clinical situations in which NPWTi may be appropriate are shown in Table 3. NPWTi has been used to treat infected wounds containing orthopedic implants in Europe, but in the US this is an off-label use. There are also several conditions in which we believe the use of NPWTi is contraindicated, although the majority of these arise from contraindications for standard NPWT (Table 4). These are listed in the manufacturers’ instruction of use. The main difference is that NPWTi should not be used in thoracic or abdominal cavities or for flaps or grafts.

#### Therapy Parameters of NPWTi

#### Panel Recommendation 2

The dwell time should range from 10 to 20 minutes, and the negative pressure time should be 2 to 4 hours at a pressure of $-125 \text{ mmHg}$, although times of up to 6 hours may be needed for larger wounds.

An NPWTi cycle comprises 3 phases: instillation of the wound with a solution, a holding period for such as debridement and systemic antibiotics.
the solution known as dwell time, and a negative pressure period. Instillation time is predicated on the instillation volume required to fill a wound or cavity and typically takes 5-30 seconds. The V.A.C. VeraFlo™ Therapy system has a Fill Assist Tool available that permits the clinician to determine an appropriate instillation volume (between 6 mL and 500 mL), which can be programmed for each cycle. The volume of topical wound solution to be instilled initially depends on the size of the dressing selected and number of pieces (1 or 2), but should be modified according to the actual amount of foam sculpted to match wound topography, including tunneling and undermining.

Using agar-based models that simulate both simple and more complex wounds (e.g., with extensive wound tunneling) and an aqueous methylene blue solution (as a visual aid), uniform coverage of the wound bed was demonstrated after a 10-minute dwell time, with an absolute coverage of about 73%. Absolute coverage increased with successive cycles. In complex wounds, application of three instillations (dwell time: 10 minutes) also showed complete penetration to the undermined and tunneled areas. In contrast, continuous instillation did not achieve complete coverage for simple or complex wounds. We therefore recommend that dwell time should be 10 minutes, with a maximum of 20 minutes based on the agar models.

The final portion of the NPWTi cycle is the application of negative pressure. No studies have specifically investigated whether there is an optimal time over which to apply negative pressure, although the majority of published studies have reported using between 2 hours and 4 hours (Table 1). Based on currently available data, we recommended that the negative pressure period be 2–4 hours, or up to 6 hours for larger wounds. Although the optimal negative pressure setting has not been studied adequately, we recommend the widely adopted -125 mmHg (Table 1) based on available data.

Once the decision has been made to initiate NPWTi, there is no advantage to delaying the treatment. After appropriate wound cleansing and surgical debridement, the clinician should fit the appropriate dressing and initiate NPWTi. NPWTi is not a substitute for appropriate medical and surgical care, nor is it a debridement modality by itself. Clinicians should assess the wound at every dressing change. The primary criteria for discontinuing NPWTi use are: 1) sufficiently robust granulation present in the wound bed such that primary closure can be achieved; 2) the wound has reached a stage such that it can be covered with a flap or graft; or 3) it is appropriate to resume conventional NPWT to further reduce the wound area. If clinicians elect to monitor the wound’s microbial status, treatment probably can be discontinued when quantitative culture results demonstrate little or no growth, and the wound is granulating. NPWTi should be discontinued if gross soft tissue or bone infection occurs, as these will need to be treated by surgical techniques in conjunction with systemic antibiotics.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rationale</th>
</tr>
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<tbody>
<tr>
<td>Untreated osteomyelitis, necrotic tissue with eschar present</td>
<td>NPWTi does not replace debridement; sources of infection must be considered</td>
</tr>
<tr>
<td>Non-enteric or unexplored fistulas</td>
<td>Possibility of communication with underlying vulnerable organs</td>
</tr>
<tr>
<td>Wound malignancy</td>
<td>May stimulate proliferation of malignant cells</td>
</tr>
<tr>
<td>Exposed blood vessels, anastomotic sites, organs, or nerves</td>
<td>NPWT can cause damage or rupture vessels due to the force of negative pressure</td>
</tr>
<tr>
<td>Use in thoracic or abdominal cavities</td>
<td>Potential risk for altering core body temperature or fluid retention within cavity</td>
</tr>
<tr>
<td>Unstable structures (e.g., flaps or grafts)</td>
<td>Periodic negative pressure or topical wound solution may be harmful for certain kinds of flaps/grafts</td>
</tr>
<tr>
<td>Patients at increased risk of bleeding</td>
<td>Follows general contraindications for NPWT</td>
</tr>
</tbody>
</table>

Table 4. Conditions when use of NPWTi is not recommended.
NPWTi Solution Selection

Panel Recommendation 3

Normal saline is the preferred solution for NPWTi.

When NPWTi was first introduced, the primary active ingredients of instillation solutions were antibiotics. Because of concerns about driving pathogen resistance, there was a gradual switch to antiseptics and other topical solutions (Table 5). However, four studies,\(^{26,27,32,35}\) including a small and large case series,\(^{27}\) a retrospective cohort study,\(^{32}\) and an RCT\(^{35}\) demonstrated that instillation of normal saline can achieve comparable outcomes to other types of solution. Selecting an instillation solution should be largely based on its tolerability, spectrum of activity, availability, and cost. Given that normal saline is inexpensive and safe, and one recent RCT suggested it is as effective as Prontosan with NPWTi, we believe this should be the first-line solution in most instances, particularly in light of wound adherence when Protonsan is used with the VeraFlo™ Therapy System, subsequently requiring surgical debridement to remove it from the wound. If normal saline does not achieve the desired result, based on pre- and post-debridement and post-instillation culture results, or inspection of the wound bed shows unsatisfactory granulation response, we suggest switching to another topical solution, such as Dakin’s (sodium hypochlorite), PHMB (polyhexamethylene biguanide), dilute acetic acid, or Sulfamylon (mafenide acetate). However, even though studies have demonstrated the antimicrobial effectiveness of acetic acid\(^{48}\) and Sulfamylon,\(^{49}\) there are no well-designed, published NPWTi studies using these agents, nor has the FDA evaluated them as antimicrobials. Moreover, Sulfamylon is expensive, has been primarily used in burns, and has some evidence to suggest it may delay healing in chronic wounds.\(^{50}\) PHMB is one of the solutions most commonly used in studies of NPWTi, often in the form of Prontosan® Wound Irrigation Solution (B. Braun Medical Inc., Bethlehem PA), which also contains betaine, a surfactant. While PHMB has been reported as being better tolerated than several other solutions by patients with chronic wounds,\(^{51}\) it has been classified recently by the European Chemicals Agency as H351, suspected of causing cancer.\(^{52}\) However, as pointed out by Gupta et al.,\(^{53}\) because the European classification of PHMB as a category 2 carcinogen only applies to PHMB as a raw material and preparations containing 1.0% or more, this ruling does not affect Prontosan® as it contains only 0.1% of PHMB.

Technical Pearls

NPWTi Dressing Application

The V.A.C. VeraFlo™ Dressing should be sculpted to fit the typography of the wound, but the surgeon should not perform the cutting over the wound in order to avoid

<table>
<thead>
<tr>
<th>Active Agents</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Antibiotics, including vancomycin, gentamycin, tobramycin, polymyxin B, bacitracin, neomycin,</td>
<td>Off-label use in USA; unknown risks and lack of consensus on their use</td>
</tr>
<tr>
<td>Silver nitrate</td>
<td>Possible systemic risks with associated logistical challenges</td>
</tr>
<tr>
<td>Normal saline</td>
<td>Recommended as a first-line solution by this panel</td>
</tr>
<tr>
<td>PHMB</td>
<td>Generally well tolerated and effective; suspected of being carcinogenic in Europe</td>
</tr>
<tr>
<td>Dakin’s solution</td>
<td>Effective antimicrobial agent and safe if concentrations kept low (e.g., 0.025%)</td>
</tr>
<tr>
<td>Microcyn (hypochlorous acid and sodium hypochlorate)</td>
<td>Electrolyzed sodium chloride solutions appear to have same benefits as Dakin’s solution, but strong evidence still needed for efficacy</td>
</tr>
<tr>
<td>Dilute Acetic acid</td>
<td>Considered effective and safe at 1% but lacking strong evidence for use in NPWTi</td>
</tr>
<tr>
<td>Sulfamylon (mafenide acetate)</td>
<td>Expensive; far less experience in wounds than burns; more evidence needed to clarify interference with wound healing</td>
</tr>
<tr>
<td>Chlorhexidine</td>
<td>Lacking evidence for use in NPWTi</td>
</tr>
<tr>
<td>Dilute Betadine</td>
<td>Lacking evidence for use in NPWTi; possibility of sensitivity and allergic reaction</td>
</tr>
</tbody>
</table>

Table 5. Solutions that have been used with NPWTi.
small pieces becoming entrapped. Loose pieces should be removed before insertion by gently rubbing the freshly cut edges of the foam. The foam should be loosely packed to fill the confines of the wound, while avoiding packing it tightly or stuffing it into the wound. The wound should be covered with the drape. For the V.A.C. VeraFlo\textsuperscript{TM} Therapy System, depending on whether the clinician selects a single V.A.C. VeraT.R.A.C.\textsuperscript{TM} pad or V.A.C.VeraT.R.A.C. Duo\textsuperscript{TM} Tube Set, one or two round holes 2.5 cm in diameter should be cut out of the drape, and the connections should be secured to the negative pressure source and instillation module. In general, the decision to use the Duo\textsuperscript{TM} Tube Set will depend on the size of the foam, the use of one or two pieces, and the geometry of the wound. Although the clinician can construct bridges between two pieces, using the Duo\textsuperscript{TM} Tube Set may be preferable. If the wound is on an area of dependent pressure (i.e., heel, sacral ulcer, other pressure ulcers) the clinician should use the bridging technique for the V.A.C.VeraT.R.A.C.\textsuperscript{TM} Pad.

**Timing of NPWTi and ancillary procedures**

When the clinician is seeing a newly referred patient for the first time, the normal procedure is to take tissue samples for culture, followed by wound debridement in the operating room and application of NPWTi. The surgeon should usually carry out dressing changes every 2–3 days but not less than three times per week, unless the wound is to be closed when cultures are sterile, in which case more frequent changes may be necessary. The clinician can perform the dressing change at the bedside with the consideration of the use of pain management. While debridement should be aggressive (i.e., removal of all infection sources as part of the debridement process), extensive operative debridement does not necessarily provide adequate immediate reduction in wound planktonic bioburden.\textsuperscript{54} Biofilms can be visualized using techniques including tissue/cellular staining, microscopy, and autofluorescence imaging. However, there is controversy regarding the need for biofilm visualization, and many medical centers do not yet have the equipment or training for biofilm characterization. Nevertheless, if the tools for this process are available and infection is persistent, visualizing biofilm can be valuable in determining its nature and in guiding which instillation solution and systemic antibiotics might be the most useful.

**Perceived Barriers and Resolutions**

Defining outcomes for successful wound care is likely to vary depending upon the clinical characteristics of the wound and the patient. Expected outcomes might not be complete wound healing, and in those cases, NPWTi might be seen as an interim treatment mode. A useful clinical outcome is successful partial wound healing with robust granulation, making the wound ready for the final surgical procedure (e.g., flap, split thickness skin graft) or next wound healing technique (e.g., NPWT).

Although NPWTi has been used for at least 12 years in many acute care settings, it still requires adequate training for nursing staff, especially in regard to identifying leaks.Leaks can be fixed by patching with an adherent dressing in most instances. Patients should be educated in regard to NPWTi, as they can be a first-line source for reporting both leaks and unit alarms. In general, nurses need to check that the physician orders are clear in regard to the type of topical wound solution and dose, as most of the other parameters will be set in the operating room.\textsuperscript{47} Training of residents regarding when and how to write NPWTi orders is also crucial. Most importantly, clinicians need to take a proactive role in ensuring that they have ordered solution bags before the NPWTi unit runs out.

Panel members’ collective experiences are that caring for the NPWTi system during the night shift in the medical center is the most problematic time; often staff members lack experience with the system and do not have expertise readily available. We recommend that if a problem arises that cannot be solved, the staff should convert NPWTi to continuous suction mode. In addition, as is the case with NPWT, NPWTi can be suspended and wet-to-wet dressing changes substituted for a period of time.
Large wounds sometimes present particular challenges (e.g., when to use more than one T.R.A.C. pad). For some wounds, placing a large foam piece at opposite ends of the wound and placing the T.R.A.C. pad at the center of each foam piece may suffice. Under these circumstances, switching connections periodically to allow the instillation point to change in reference to the wound geometry can be useful.

**Areas of Future Exploration**

Although the mechanisms of action of NPWT have been largely elucidated, further research is needed to determine whether they are similar for NPWTi, or if we should consider additional mechanisms of action. Data from full-thickness excisional animal models suggest that NPWTi with saline instillation may be significantly better than NPWT in improving the rate of wound granulation. However, these results are to some extent confounded by the use of different types of dressing foams, mechanical properties and hydrophobicity, and the studies need to be repeated in human patients. Microdeformation may be important to both NPWT and NPWTi in respect to the increase in various biochemical factors that are elicited. Recent research conducted in full-thickness excisional animal models suggests while gene grouping and protein expression is similar between the two modes, there may be some important differences. These differences include several genes and entities such as integrins alpha 3 and beta 6, EGF (epidermal growth factor) and EGF receptor, and vitronectin. Thus, while some of the differences observed in studies between NPWT and NPWTi might be due to the nature of the instillation solution, which facilitates loosening of soluble debris and expeditious removal of exudate and bioburden, other cellular factor influences may also be at work.

In particular, we need further research to determine the solutions to use with NPWTi, and the appropriate clinical applications for each solution. In that context, the results of a recent randomized controlled trial comparing surrogate outcomes of instilling normal saline versus 0.1% polyhexanide + 0.1% betaine with NPWTi as an adjunctive treatment for infected wounds that required hospital admission and operative debridement suggest that 0.9% normal saline may be as effective as an antiseptic for NPWTi. Finally, although we have outlined updated recommendations in regard to cycle parameters, including dwell time, negative pressure time and pressure, we still lack published research that can inform whether these recommendations are generalizable, or if there may be clinical situations in which we should make exceptions.

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As with any case study, the results and outcomes should not be interpreted as a guarantee or warranty of similar results. Individual results may vary depending on the patient's circumstances and condition.

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