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INVITED REVIEW

Clinical recommendations and practical guide for negative pressure wound therapy with instillation

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Abstract

Effective wound management involves a comprehensive assessment of the patient and the wound to determine an optimal wound treatment plan. It is critical to identify and address factors that may impair wound healing, prior to selecting the most appropriate therapy for each patient. Negative pressure wound therapy (NPWT) is a well-established advanced therapy that has been successful in adjunctive management of acute and chronic wounds. In recent years, the introduction of topical wound solution delivery in combination with NPWT has provided further benefits to wound healing. A commercially available system now offers automated, volumetric control of instilled topical wound solutions with a dwell time in combination with NPWT (NPWTi-d; V.A.C. VeraFlo™ Therapy, KCI, an Acelity company, San Antonio, TX). This NPWTi-d system differs from other instillation systems in that a timed, predetermined volume of topical wound solution is intermittently delivered (versus continuously fed) and allowed to dwell in the wound bed (without NPWT), for a user-selected period of time before NPWT is resumed. This added accuracy and process simplification of solution delivery in tandem with NPWT have prompted use of NPWTi-d as first-line therapy in a wider subset of complex wounds. However, considerably more research is required to validate efficacy of NPWTi-d in various wound types. The purpose of this review is to provide a relevant overview of wound healing, describe current literature supporting the adjunctive use of NPWTi-d, propose a clinical approach for appropriate application of NPWTi-d and conclude with case studies demonstrating successful use of NPWTi-d. Based on this review, we conclude that either a large case series examining effects of NPWTi-d on different wound types or possibly a large prospective registry evaluating NPWTi-d with real-world topical wound solutions versus immediate debridement and closure would be valuable to the medical community in evaluating the efficacy of this promising therapy.

Introduction

It is recognised that effective wound management requires a comprehensive assessment of both the patient and the wound to determine the optimal treatment plan for achieving wound care goals. Numerous wound and patient risk factors are known to potentially complicate wound healing and increase health care costs (Table 1) (1,2). Wounds at risk for delayed healing include

Key Messages

- effective wound management involves a comprehensive assessment of the patient and the wound to determine an optimal wound treatment plan
- negative pressure wound therapy (NPWT) is a well-established advanced therapy that has been successful in the adjunctive management of acute and chronic wounds

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- a commercially available system now offers automated, volumetric control of instilled topical wound solutions with a dwell time in combination with NPWT (NPWTi-d)
- the purpose of this review is to provide a relevant overview of wound healing, describe current literature supporting adjunctive use of NPWTi-d, propose a clinical approach for appropriate application of NPWTi-d and conclude with case studies demonstrating successful use of NPWTi-d
- we conclude that either a large case series examining the effects of NPWTi-d on different wound types or possibly a large prospective registry evaluating NPWTi-d with real-world topical wound solutions would be valuable to the medical community in evaluating the efficacy of this promising therapy

those with extensive tissue loss, critical colonisation and/or infection, high levels of exudate or exposed critical structures. Historical factors, including the duration the wound has been open, the number of times it has been open and previous attempts to close the wound, help define the timeline until closure. Debridement, antibiotic treatment and local application of antiseptics or antimicrobials, delayed primary closure (when necessary), use of drains and repeated wound cleansing are fundamental concepts in caring for these at-risk wounds.

Compared with swabbing or bathing, wound irrigation is considered to be the most consistent and effective method of wound cleansing (3). Critical to the process of wound healing, wound irrigation is the steady flow of a solution across an open wound surface to achieve wound hydration, remove deep debris and assist with visual examination. The irrigation solution is meant to remove cellular debris, wound exudate and metabolic wastes to help create an optimal wound healing environment (4,5).

Negative pressure wound therapy (NPWT) is a tool commonly used to assist in preparing larger at-risk wounds for delayed closure. Porcine studies have shown that NPWT increased local blood flow and the rate of granulation tissue formation (6–8). While NPWT has been shown to speed up wound closure rates compared with standard wound care dressings (9–11), bioburden control is not a proven benefit of NPWT (12–15). In one study, NPWT was shown to reduce non-fermentative Gram-negative bacilli, although wounds culturing *Staphylococcus aureus* had increased bacterial levels over time with NPWT (13). Other studies have shown that NPWT improves local wound appearance in a porcine infected wound model, despite increasing bioburden (16). Additional limitations of conventional NPWT include difficulties in clearing thick exudates through the foam, as well as painful dressing removal.

All of these factors have led to combining the therapies of NPWT and solution instillation with a dwell time (NPWTi-d) to adjunctively treat at-risk wounds that would benefit from vacuum-assisted drainage and controlled repeated delivery of topical wound solutions, such as normal saline and wound cleansers. For the purposes of this review, NPWTi-d refers to the combination technology delivered historically as V.A.C. Instill® Wound Therapy with a reticulated open cell foam (ROCF) dressing (ROCF-G; V.A.C.® GranuFoam™ Dressing; KCI, an Acelity company, San Antonio, TX) or currently as VA.C. VeraFlo™ Therapy (KCI) using ROCF-V (V.A.C. VeraFlo™ Dressing, KCI), which is specifically designed for instillation therapy.

Table 1 Wound healing risk factors [adapted from Riou. et al. (1) and Abbas and Hill (2)]

- Age >65 years
- Wound infection
- Pulmonary disease
- Vascular disease
- Haemodynamic instability
- Ostomies
- Hypoalbuminaemia
- Systemic infection
- Obesity
- Uraemia
- Hyperalimentation
- Ascites
- Pharmacological perturbations
- Nutritional deficiencies of specific vitamins/minerals
- Malignancy
- Hypertension
- Length and depth of incision
- Foreign body in the wound
- Anaemia
- Jaundice
- Diabetes – poor control
- Active smoker
- Type of injury
- Radiation therapy
- Steroid use
- Iatrogenic factors (e.g. stress, chemical, mechanical, repeated trauma and impaired cognition)

NPWTi-d differs from irrigation and lavage in that the instilled fluid is slowly introduced into the wound and remains in the wound bed for a defined period of time before being removed by applying negative pressure. Automated instillation creates a controlled, protected environment for flushing and cleansing wounds by the proposed mechanism of loosening soluble contaminants in the wound bed followed by subsequent removal during NPWT. As a result, the planktonic bacterial burden can be decreased, contaminants removed and the wound thus cleansed, without manual intervention. In addition, instillation with NPWT can also lower wound fluid viscosity, which in turn facilitates more efficient removal of exudates and infectious material through the foam and into the canister (17–19).

Enhanced granulation tissue production has been reported with use of NPWTi-d with saline instillation versus conventional NPWT in several comparative studies (20,21). Kim *et al.* reported fewer operative visits, shortened time to final surgical procedure, shorter hospital length of stay and greater percentage of wounds closed before discharge with NPWTi-d with polyhexanide instillation versus NPWT (22). Easier and less painful dressing changes with NPWTi-d versus NPWT have also been noted (23).

The literature contains descriptions of continuous, gravity-fed solution irrigation with NPWT, as well as automated, controlled, intermittent solution instillation with NPWT, such as the NPWTi-d system described in this review. In an agar-based model study, NPWT with automated, volumetrically controlled instillation of solutions showed significantly more uniform coverage of the entire simulated wound bed and increased solution exposure with repeated cycles of instillation, compared with continuous, gravity-fed irrigation with NPWT, but these results have not yet been confirmed clinically (19).

A recently convened consensus panel of expert users recommended use of NPWTi-d as an adjunctive therapy in acutely and chronically infected wounds, contaminated wounds, diabetic wounds, traumatic wounds, decubitus wounds, wounds with exposed bone, wounds with underlying osteomyelitis and painful wounds and as a bridge between staged/delayed amputations (24). Other authors have recommended consideration of NPWTi-d in wounds with high levels of exudate and slough content, as well as acute traumatic wounds or acutely debrided wounds due to underlying infection (25).

This publication will provide a relevant overview of wound healing, describe the current literature supporting the adjunctive use of NPWTi-d, provide a clinical approach for appropriate application of NPWTi-d and conclude with case studies demonstrating the successful use of NPWTi-d.

Wound healing management

Wounds heal either by primary, secondary or tertiary intention. Closure by primary intention occurs if there is no loss of tissue, or when the wound is surgically closed immediately following the injury by direct approximation of the wound margins or by graft or flap (26). Typically, this type of wound is closed within 6 hours of injury. Secondary intention (or closure by secondary intent) refers to healing, without surgical intervention, of a wound that is intentionally left open because of the presence of infection, excessive trauma or loss of tissue with separated edges of the wound. Closure occurs when wound edges come together via granulation tissue formation and subsequent epithelialisation (27).

Tertiary intention (delayed primary closure) occurs when a wound is initially left open after removal of all non-viable tissue. Wound edges are surgically brought together after a period of open observation, when the wound appears clean and well vascularised. Tertiary intention can also refer to subsequent surgical repair of a wound initially left open or not previously treated. This method is indicated for infected or unhealthy wounds with high bacterial content, wounds with a lengthy time lapse since injury or wounds with a severe crush component with significant tissue devitalisation (26,28).

NPWTi-d is a tool primarily suited for wounds that are being prepared for delayed primary closure, by either surgical or non-surgical closure, depending on goal of therapy: cleansing (e.g. removal of infectious material and other wound debris) and/or granulation tissue formation.

Wound infection management

Control and prevention of infections is critical in order for the normal wound healing stages to occur. When wound surface bacteria begin replication and increase their metabolic activity, the resulting by-products, such as endotoxins and metalloproteinases, negatively impact all phases of wound healing (29). The presence of bacteria in the wound bed can be divided into four distinct categories based on the induced host response. These categories are termed contaminated, colonised, critically colonised and infected. All wounds are contaminated at first, and progress up and down the wound bioburden continuum depending upon the quantity and types of microorganisms present in the wound:

- *Contaminated* is defined as the presence of non-replicating microorganisms within a wound.
- *Colonised* refers to replicating microorganisms that adhere to the wound surface but do not cause cellular damage to the host. Colonised wounds are those making progress towards healing; bioburden does not impair the wound's ability to heal.
- The term *critically colonised*, also synonymous with *locally infected*, was introduced to describe a wound with an increasing level of bacterial burden that is intermediate between the category of *colonisation* and *infection*. Wounds that are critically colonised will not heal but may not display classic signs of infection. They are at a very high risk to become infected. A confounding factor in the stalling process may be the presence of biofilms, which can give the wound a healthy pink appearance even though the wound may contain large colonies of bacteria (30).
- *Infection* occurs when there is a histological demonstration of tissue invasion by organisms and a subsequent host response (31). Infected wounds may demonstrate any of the classic clinical signs of infection; biofilms may be present with soft tissue infection and peri-wound extension. Type and pathogenicity of the organisms may sometimes be as important as quantity in terms of increasing the risk of infection (32).

The combined regular cleansing and applied negative pressure of NPWTi-d are likely of greatest benefit in critically colonised or infected wounds.

Wound bed preparation

Wound bed preparation is defined as the comprehensive management of the wound to accelerate endogenous healing by eliminating negative factors that prevent wound healing (31,33,34). This process often involves management of necrotic tissue, infection/inflammation and moisture balance for wound healing. Wound bed preparation is most important for wounds with excessive tissue loss, when the strategy is to close the wound by secondary intention, or when wounds need to be prepared for grafts, such as split-thickness and epidermal skin grafts. Standard NPWT has been shown to promote granulation tissue formation in diabetic foot ulcers (35) and diabetic foot wounds (36) compared with advanced moist wound dressings. Findings in more recent studies have suggested improvements in granulation tissue formation with NPWTi-d (20,21) that are similar to results noted in preclinical porcine models (37,38). However, preclinical results have yet to be confirmed in human studies.

Mechanisms of action

The mechanisms of action (MOA) for NPWT are well established and include both mechanical (macrostrain) and biological (microstrain) tissue responses (39–43). The macrostrain benefits include drawing the wound edges together, promoting perfusion, reducing oedema and removing infectious material from the wound bed. The benefits of microstrain

include promoting granulation tissue formation via cell micro-deformation that stimulates metabolic activity and cellular proliferation (39). Combining NPWT with topical wound instillation provides further advantages for wound healing. Instillation and dwell of a topical wound solution allows thorough coverage of the wound bed, thereby cleansing the wound. The topical wound solution that is allowed to dwell over the wound bed also has the potential to dilute and solubilise infectious materials, devitalised tissue and slough. Pain and discomfort may be reduced either by using an appropriate concentration of a topical anesthetic solution during the dwell time or by soaking the dressing with solution prior to removal.

Review of instillation evidence

Clinical evidence

In recent years, NPWTi-d has been increasingly used as an adjunctive treatment for acute and chronic wounds. Single-centre case series studies and a few semi-randomised trials have been performed. While none of these studies constitutes level 1 evidence, they do provide significant guidance on the clinical role of NPWTi-d on the types of wounds described. The evidence is reviewed below and summarised in Table 2.

A retrospective analysis was recently published by Gabriel *et al.* (44) that compared clinical outcomes of wounds treated with NPWTi-d versus NPWT and then further estimated cost differences between the treatments. Data were extracted from records of patients with extremity or trunk wounds treated with NPWT ($n = 34$) or NPWTi-d ($n = 48$). Wounds were debrided and systemic antibiotics were administered prior to any therapy. For patients receiving NPWTi-d, ROCF-V was placed over the wound. Saline or polyhexanide (Prontosan® Wound Irrigation Solution, B. Braun Medical Inc., Bethlehem, PA) was instilled to fill the foam with a set dwell time ranging from 1 to 60 seconds, followed by NPWT of −125 mmHg for 1 or 2 hours. For patients receiving traditional NPWT, black or silver foam (V.A.C.® GranuFoam™ Dressing, V.A.C. GranuFoam Silver™ Dressing, KCI) was placed in the wound with application of −125 mmHg continuous pressure. Dressing changes were carried out every 2–3 days for both groups. Results showed significant differences ($P < 0{\cdot}001$) between NPWTi-d and NPWT patients, respectively, for: mean operating room (OR) debridements (2·0 versus 4·4), mean hospital stay (8·1 versus 27·4 days), mean length of therapy (LOT) (4·1 versus 20·9 days) and mean time to wound closure (4·1 versus 20·9 days). Based on the outcomes data, a hypothetical economic model using cost assumptions was created to calculate cost savings for NPWTi-d (related to) number of debridements and LOT. OR debridement cost ($3393) was based on information in Granick *et al.* (45). Daily therapy cost for each modality ($194·80, NPWTi-d; $106·08, NPWT) was based on internal company information. The hypothetical economic model showed a potential average per-patient reduction of $8143 for OR debridements between NPWTi-d ($6786) and NPWT ($14 929) patients. There was also a $1418 difference in average therapy costs between the two groups ($799/NPWTi-d versus $2217/NPWT). The authors concluded that NPWTi-d appeared to assist in wound cleansing and exudate removal, which may have allowed for earlier wound closure compared with NPWT. The hypothetical economic model findings demonstrated potential cost-effectiveness of NPWTi-d compared with NPWT (44).

Kim *et al.* (22) retrospectively compared results between patients treated with adjunctive NPWT or NPWTi-d at MedStar Georgetown University Hospital. This study provides insight into the effect of length of dwell phase with a specific topical wound solution on frequency of debridement and time to closure. A total of 142 patients with acutely infected wounds were included in the analysis: 74 NPWT patients versus 34 NPWTi-d with 6-minute dwell time patients and 34 NPWTi-d with 20-minute dwell time patients. All patients in the NPWTi-d group underwent instillation with Prontosan® Wound Irrigation Solution. Both NPWT and NPWTi-d groups had continuous negative pressure at −125 mmHg. NPWTi-d groups also had either a 6-minute or a 20-minute dwell time followed by NPWT for 3·5 or 2 hours, respectively. Patients in both NPWTi-d groups had significantly fewer operative visits compared with those treated with standard NPWT: 6-minute dwell group, $P = 0{\cdot}043$; 95% confidence interval (CI), 0·014–0·75 and 20-minute dwell group, $P = 0{\cdot}003$; 95% CI, 0·19–0·93. Overall, the 20-minute dwell time group had significantly lower length of hospital stay compared with the NPWT group ($11{\cdot}4 \pm 5{\cdot}1$ versus $14{\cdot}92 \pm 9{\cdot}2$ days, respectively; $P = 0{\cdot}034$). Both NPWTi-d groups also required significantly fewer days to final surgical procedure compared with the NPWT group (6-minute dwell time: $P = 0{\cdot}043$; 95% CI, 0·0651–4·04 and 20-minute dwell time: $P = 0{\cdot}0019$; 95% CI, 0·39–4·36, respectively). Compared with those in NPWT group, patients treated with NPWTi-d in the 6-minute dwell group had significantly higher percentage of wounds that: (i) closed prior to discharge (94% versus 62%; $P \leq 0{\cdot}001$) and (ii) showed culture improvement for Gram-positive bacteria (90% versus 63%; $P \leq 0{\cdot}001$).

A prospective pilot study by Goss *et al.* (15) evaluated the efficacy of wound bed preparation using sharp surgical debridement followed by either NPWT or NPWTi-d. A total of 13 patients with 16 chronic lower leg and foot wounds requiring surgical debridement were included in this study. Patients were enrolled sequentially into two groups: sharp surgical debridement followed by NPWT for 1 week or sharp surgical debridement followed by NPWTi-d for 1 week. All patients treated with NPWTi-d had instillation of quarter-strength Dakin's solution (Century Pharmaceuticals, Inc., Indianapolis, IN) with a 10-minute dwell time, followed by 1 hour of NPWT. Quantitative cultures were taken preoperatively and postoperatively. In the immediate post-debridement samples, there was a mean of three different types of bacteria per wound. In these samples, the NPWTi-d group had a statistically greater mean colony-forming unit (CFU)/gram tissue culture compared with standard NPWT group ($3{\cdot}7 \times 10^6 \pm 4 \times 10^6$ versus $1{\cdot}8 \times 10^6 \pm 2{\cdot}36 \times 10^6$, respectively, $P = 0{\cdot}016$). However, at the end of 7 days of therapy, no statistical difference between the two groups was found. Although not statistically significant, wounds treated with NPWTi-d had a lower mean CFU/gram of tissue culture compared with NPWT ($2{\cdot}6 \times 10^5 \pm 3 \times 10^5$ versus $2{\cdot}79 \times 10^6 \pm 3{\cdot}18 \times 10^6$, respectively, $P = 0{\cdot}43$). However, the NPWTi-d group had an overall reduction in CFU, while the NPWT group had an overall increase in CFU. Results from

Table 2 Literature review of NPWTi-d (clinical evidence)

Author	Study type and patients	Instillation therapy parameters	Results/conclusions
Gabriel *et al.* (44)	• Retrospective analysis comparing NPWT ($n=34$) and NPWTi-d ($n=48$) patients • Hypothetical economic model using cost assumptions for debridement and LOT to compare NPWT and NPWTi-d patients	• NPWT: −125 mmHg, continuously • NPWTi-d - Instillation of saline or polyhexanide with a range of 1- to 60-second dwell time, followed by 1 or 2 hours of NPWT, continuously	• Results showed significant differences ($P<0{\cdot}001$) between NPWTi-d and NPWT patients, respectively, for: - mean OR debridements (2·0 versus 4·4) - mean hospital stay (8·1 versus 27·4 days) - mean LOT (4·1 versus 20·9 days) - mean time to wound closure (4·1 versus 20·9 days) • The hypothetical economic model showed a potential average reduction of $8143 for OR debridements between NPWTi-d ($6786) and NPWT ($14 929) patients • There was also a $1418 difference in average therapy costs between the two groups ($799/NPWTi-d versus $2,217/ NPWT)
Kim *et al.* (22)	• Retrospective historical cohort controlled study comparing NPWT and NPWTi-d was performed at a single institution • NPWT group: 74 patients • NPWTi-d 6-minute dwell group: 34 patients • NPWTi-d 20-minute dwell: 34 patients	• NPWT: −125 mmHg, continuously • NPWTi-d - Instillation of Prontosan with 6-minute dwell time, followed by 3·5 hours NPWT at −125 mmHg, continuously - Instillation of Prontosan with 20-minute dwell time, followed by 2 hours NPWT at −125 mmHg, continuously	• Patients receiving NPWTi-d (6- and 20-minute dwell) had significantly fewer operative visits compared with NPWT patients ($P=0{\cdot}043$; 95% CI, 0·014–0·75; $P=0{\cdot}003$; 95% CI, 0·19–0·93, respectively) • Overall, 20-minute dwell time group had significantly shorter length of hospital stay compared with NPWT group ($11{\cdot}4\pm5{\cdot}1$ versus $14{\cdot}92\pm9{\cdot}2$, respectively; $P=0{\cdot}034$) • Both NPWTi-d groups required significantly fewer days to final surgical procedure compared with NPWT group ($P=0{\cdot}043$; 95% CI, 0·0651–4·04; $P=0{\cdot}0019$; 95% CI, 0·39–4·36, respectively) • Compared with those in NPWT group, patients treated with NPWTi-d in the 6-minute dwell group had significantly ($P\leq0{\cdot}001$) higher percentage of wounds: (i) closed prior to discharge (94% versus 62%) and (ii) culture improvement for Gram-positive bacteria (90% versus 63%)
Goss *et al.* (15)	• Prospective pilot study evaluating the efficacy of wound bed preparation with sharp surgical debridement and NPWT versus sharp surgical debridement and NPWTi-d • 13 patients with 16 chronic lower leg and foot wounds were sequentially enrolled at random into two treatment groups: - NPWT: eight wounds - NPWTi-d: eight wounds	• Both groups received operative debridement • NPWT: −125 mmHg, continuously • NPWTi-d: instillation of quarter-strength Dakin's solution with a 10-minute dwell time, followed by 60 minute of NPWT at −125 mmHg, continuously	• The NPWTi-d group had a statistically greater mean colony-forming unit (CFU)/gram tissue culture compared with standard NPWT group ($3{\cdot}7\times10^6\pm4\times10^6$ versus $1{\cdot}8\times10^6\pm2{\cdot}36\times10^6$, respectively, $P=0{\cdot}016$) • However, at the end of the 7-day therapy duration, no statistical difference between the two groups was found • Although not statistically significant, wounds treated with NPWTi-d had a lower mean CFU/gram of tissue culture compared with NPWT ($2{\cdot}6\times10^5\pm3\times10^5$ versus $2{\cdot}79\times10^6\pm3{\cdot}18\times10^6$, respectively, $P=0{\cdot}43$) • However, the NPWTi-d group had an overall reduction in CFU, while the NPWT group had an overall increase in CFU • Results from this study support the use of NPWTi-d using quarter-strength Dakin's solution in the management of bioburden for 7 days following sharp debridement

Table 2 Continued

Author	Study type and patients	Instillation therapy parameters	Results/conclusions
Brinkert *et al.* (20)	• Prospective case series to evaluate the outcomes of 131 patients with complex wounds treated with NPWTi-d	• Instillation of saline with a 10-minute dwell time, followed by 4–12 hours of NPWT at −125 mmHg, continuously	• Wound closure was achieved in 128 of 131 (98%) wounds • No incidence of wound recurrence or dehiscence was observed at operated site • With respect to filling dead space more rapidly and completely, NPWTi-d using saline showed improved granulation tissue production compared with NPWT
Fluieraru *et al.* (21)	• Retrospective case series of 24 patients - 12 patients who had been unsuccessfully treated with NPWT - 12 patients with complex wounds	• Isotonic saline was instilled for 30 seconds, followed by a 10-minute soak time and continuous negative pressure at −125 mmHg every 4 hours • Dressing changes were performed every 3 days • Instillation therapy was used to complete surgical debridement and promote a reaction after conventional NPWT	• Prior to instillation, all patients were surgically debrided. • Mean duration of instillation therapy was 10·1 ± 4·0 days (range 6–15 days) • All but one patient healed following surgical closure • Patient who failed to recover had a lower extremity that was too devascularised to granulate efficiently • Main observed effects of instillation therapy in these patients included promotion of granulation tissue formation and filling of undermined cavities
Wolvos (46)	• Pilot study of consecutive case series with seven patients	• Instillation solutions used were: Microcyn®, Dakin's Solution® (quarter strength) • Instillation therapy occurred every 2–4 hours including a 5- to 10-minute soak time and continuous negative pressure with settings at −100 to −125 mmHg	• Six of seven patients received NPWTi-d, one patient was treated with NPWT only • Overall length of therapy ranged from 7 to 54 days • Wounds were closed by primary, secondary, delayed primary intention or an STSG • No complications occurred in this case series

CI, confidence interval; LOT, length of therapy; NPWT, negative pressure wound therapy; NPWTi-d, dwell time in combination with NPWT; OR, operating room, STSG, split-thickness skin graft.

this study support the use of NPWTi-d using quarter-strength Dakin's solution in the management of bioburden for 7 days following sharp debridement.

Brinkert *et al* (20) presented a large case series evaluating the outcomes of 131 patients with complex wounds adjunctively treated with NPWTi-d using saline. A prospective case series was conducted between January 2012 and December 2012 by three French teams at three different hospitals. There were various wound aetiologies, such as open fracture, pressure ulcer and non-healing postoperative dehiscence wounds. Patients who had been treated with NPWT ($n = 46$) were also eligible to receive NPWTi-d. The remaining 85 patients received NPWTi-d as the primary therapy. Saline was instilled for 20 or 30 seconds, depending on patient conditions; dwell time was 10 minutes, followed by negative pressure (continuous at −125 mmHg) ranging between 4 and 12 hours. Mean duration of NPWTi-d was 12·19 days, and conventional NPWT was applied in 48·8% of cases after NPWTi-d until secondary closure or surgical closure was indicated. Surgical closure was performed through the use of a skin graft ($n = 74$), flap ($n = 22$) or primary suture ($n = 32$). Wound closure was achieved in 128 of 131 (98%) wounds. Incomplete wound closure in the remaining three wounds occurred because of limb ischaemia ($n = 1$) or death unrelated to therapy ($n = 2$). No incidence of wound recurrence or dehiscence was observed at the operated site. With respect to filling dead space more rapidly and completely, NPWTi-d using saline showed improved granulation tissue production compared with NPWT.

Fluieraru *et al.* (21) conducted a retrospective case series of 24 patients who had either been unsuccessfully treated with NPWT ($n = 12$) or who presented with complex wounds ($n = 12$). Prior to instillation, all patients were surgically debrided. Isotonic saline was instilled for 30 seconds, followed by a 10-minute dwell time and continuous negative pressure at −125 mmHg every 4 hours. Dressing changes occurred every 3 days. Mean duration of instillation therapy was 10·1 ± 4·0 days (range 6–15 days). All but one patient healed following surgical closure. A patient who failed to recover had a lower extremity that was too devascularised to granulate efficiently. The authors observed that instillation therapy promoted granulation tissue formation and filling of undermined cavities in these patients.

A small case series by Wolvos (46) evaluated the use of NPWTi-d ($n = 6$) and NPWT only ($n = 1$) with open, contaminated or infected wounds. NPWTi-d patients were instilled with either Microcyn® antiseptic solution (Oculus Innovative Science, Petaluma, CA) ($n = 5$) or quarter-strength Dakin's Solution® (Century Pharmaceuticals, Inc.) ($n = 1$). Instillation

parameters included a 5- to 10-minute soak time followed by continuous negative pressure of either −100 or −125 mmHg every 2–4 hours. Overall LOT ranged from 7 to 54 days and wounds were closed by primary, secondary, delayed primary intention or with the use of a split-thickness skin graft (STSG). Wound healing was achieved in all cases and no complications were observed in this case series.

Preclinical/bench study evidence

Preclinical bench and porcine studies have contributed significantly to understanding of the MOAs behind NPWTi-d. Among the benefits seen were enhanced granulation tissue formation, decreased bacterial environmental contamination and exposure of the wound bed to the instillation solution.

In 2011, Lessing *et al.* initially compared the granulation response of NPWTi-d with saline with standard NPWT in a non-infected porcine wound model and found an increase in granulation tissue formation at 7 days with NPWTi-d compared with NPWT (37). Subsequently, Lessing *et al.* (38) further investigated granulation tissue formation in this same porcine model comparing NPWTi-d with saline versus various NPWT modes [i.e. NPWT (standard foam dressing) in continuous, intermittent and dynamic modes]. Each of five female domestic swine received ten full-thickness dorsal excisional wounds that were treated with continuous NPWT (at −125 mmHg), intermittent NPWT (5 minutes at −125 mmHg followed by 2 minutes at 0 mmHg), dynamic (controlled variable) NPWT (3-minute rise to −125 mmHg followed by a controlled 3-minute fall to −25 mmHg) and NPWTi-d with saline (5-minute soak time followed by 2·5 hours of negative pressure at −125 mmHg). The swine were euthanised on day 7 and specimens were collected for histopathological review. At day 7, no difference in average granulation thickness was observed among continuous, intermittent and dynamic NPWT. However, wounds treated with NPWTi-d with saline had statistically greater average granulation thickness ($P < 0{\cdot}05$) of 44%, 57% and 40% compared with the wounds treated with NPWT in all three conditions, respectively. Compared with all NPWT-treated wounds, those treated with NPWTi-d showed a significantly greater reduction in wound area and perimeter ($P < 0{\cdot}05$) based on 3D image analyses. Wounds treated with NPWTi-d also demonstrated a faster average wound fill rate than those treated with continuous and dynamic controlled NPWT (40% and 65%, respectively, $P < 0{\cdot}05$). Data from this porcine study suggest that NPWTi-d may result in faster granulation tissue formation compared with continuous, intermittent and dynamic controlled NPWT.

An agar wound model was used to evaluate the distribution of solutions instilled continuously versus periodically using NPWTi-d (19). Continuous instillation was defined as fluid delivered continuously at a constant rate of 30 ml/hour to the wound bed for 3·5 hours, with continuous removal by negative pressure; periodic therapy instilled solutions with one to three 10-minute dwell times. NPWTi-d with ROCF-V was used with both therapies. Results showed that periodic instillation therapy demonstrated uniform distribution of solutions throughout the entire wound bed, while continuous instillation therapy displayed limited delivery of solutions throughout the wound bed. There was significantly more coverage of the wound bed when the solution was delivered using periodic versus continuous instillation ($73{\cdot}0 \pm 3{\cdot}2\%$ versus $30{\cdot}3 \pm 10{\cdot}7\%$; $P < 0{\cdot}05$). The agar wound model was also sectioned to visualise exposure of instillant to tunnelled and undermined regions. It visually appeared that following continuous instillation, there was little solution exposure to the tunnelled and undermined regions. However, following the application of three 10-minute dwell times per NPWTi-d, there was visual evidence that tunnelled and undermined regions in the model had been exposed to instilled solutions (19).

Clinical approach flow diagram

Good wound healing strategies always start with a clinical approach. In this review, we propose a clinical approach flow diagram for the consideration of NPWTi-d as part of the wound treatment strategy (Figure 1). The first step always involves a complete patient and wound assessment. Both external and internal factors affecting wound treatment must be considered at the initial assessment. The patient assessment should be thoroughly documented to allow for an interdisciplinary approach for healing the patient (47). Where available, a multidisciplinary team may help identify possible obstacles to wound healing and they may suggest patient interventions to optimise the patient for wound healing (Table 1) (1,2,47–49). The patient's nutritional and hydration status are important factors that should be stressed and addressed consistently throughout the treatment period.

A comprehensive wound assessment should be performed to determine wound size (length, width and depth), presence of infection, undermining, tunnelling sinus tracts, exudates, presence of necrotic tissue, granulation tissue status and epithelialisation. In most cases, the wound will require debridement to allow for complete wound bed assessment. In 2000, Attinger stated that, after a thorough patient assessment, the most important step to treating any wound is sufficient debridement to remove all foreign material, unhealthy, or non-viable tissue until the wound edges and base consist of only normal and healthy tissue (50). In 2013, Diefenbeck concluded that adequate surgical debridement is the prerequisite for the successful treatment of skin, soft tissue and bone tissue (51). Goss *et al.* reported that surgical wound debridement is necessary before treating infected wounds with NPWTi-d (15). Debridement leads the health care professional to develop a wound bed preparation strategy that will lead to wound closure. NPWTi-d does not replace debridement of the acutely infected, chronically infected or contaminated wound, nor does it replace appropriate antibiotic therapy (24).

A wound bed preparation strategy (Table 3) plays a key role in deciding the goal of therapy and eventual wound closure. After debridement, an active wound closure strategy can be determined based on several variables, which include tissue loss, contamination/infection, exudation, exposed critical structures, wound is stalled and so on (Table 4). Including use of NPWTi-d as part of an active wound closure strategy involves consideration of therapy goals, such as wound cleansing, wound granulation tissue formation and a combination of both, prior to delayed primary or secondary wound closure.

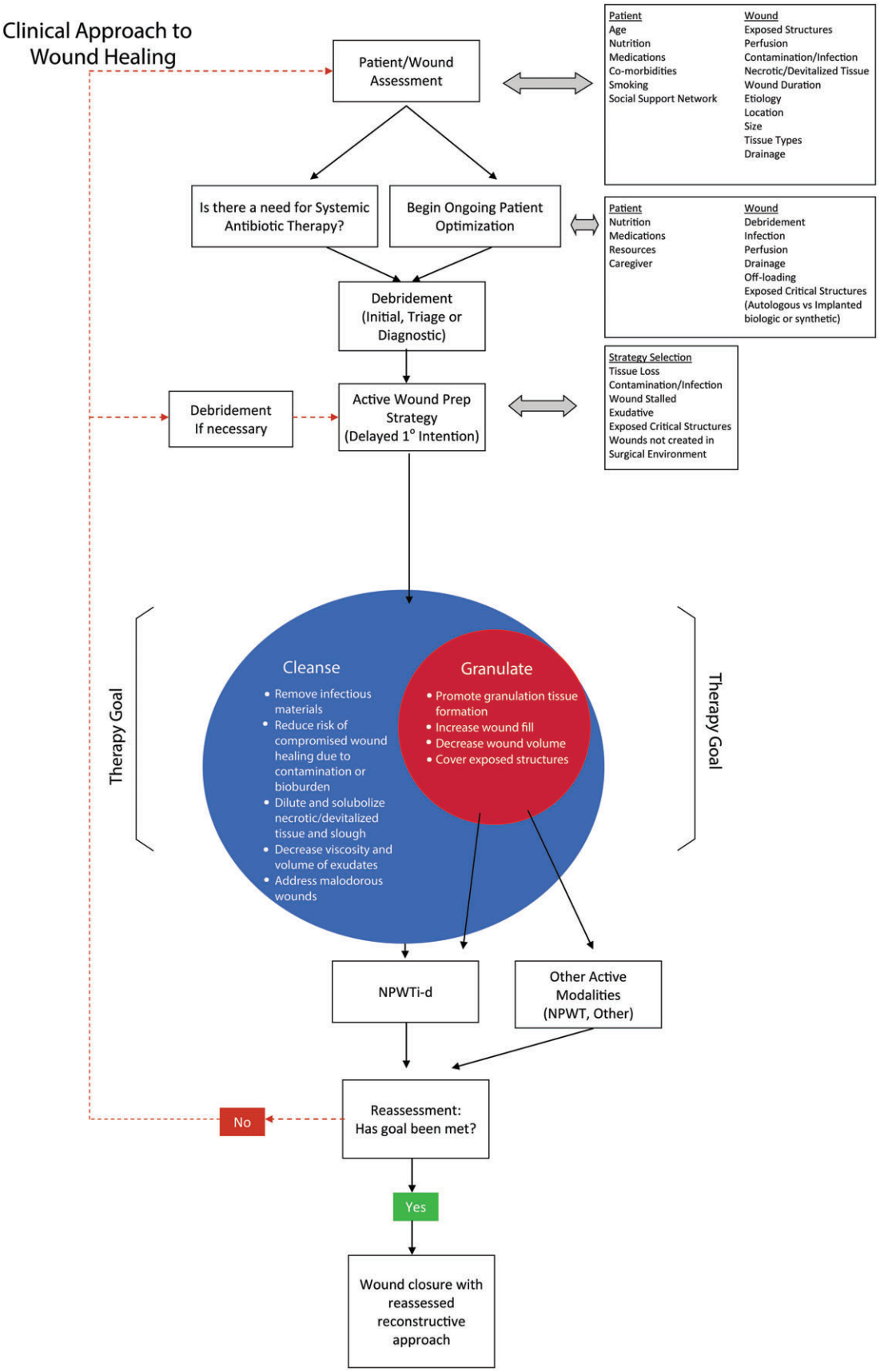

Figure 1 Clinical approach to wound healing. Reproduced with permission from KCI Licensing, Inc.

Table 3 Goals of wound bed preparation

Cleanse	Granulate
• Remove contamination/ infectious materials • Dilute and solubilise devitalised tissue • Decrease exudate	• Increase granulation preparation • Promote wound fill • Cover exposed structures

When selecting NPWTi-d to accomplish cleansing or granulation goals of therapies, the instillation solution and dressing selection should be considered. An international consensus panel convened to propose guidelines for the use of NPWTi-d based on clinical evidence and experience (24). This expert panel discussed the different topical wound solutions, with appropriate dwell and cycle times and found that Prontosan and Microcyn/Dermacyn were appropriate instillation solutions that could be used with NPWTi-d. Although concerns have been recently raised in Europe regarding the potential carcinogenic effects of polyhexamethylene biguanide (PHMB), which is one ingredient in Prontosan, the classification of PHMB as a category 2 carcinogen pertains only to PHMB as a raw material and to preparations with PHMB content of 1·0% or more. Prontosan wound irrigation solution (B. Braun Medical) contains 0·1% PHMB in addition to 0·1% betaine and purified water, and thus is not affected by the European classification.

Recent evidence suggests that normal saline (20,21) and Dakin's solution (15) are also effective and are readily available in the USA. Table 5 reviews the published evidence of topical wound solutions along with therapy parameters that have been used with instillation therapy.

Dressing selection for NPWTi-d therapy is dependent on wound characteristics of size, depth, tunnelling and undermining. The reticulated open-cell foam polyurethane ester dressings [ROCF-V and ROCF-VC (VeraFlo Cleanse™ Dressing; KCI)] are less hydrophobic dressings (compared with ROCF-G) and designed to deliver the various compatible topical wound instillation solution(s) (Table 5) to the wound site (23). In at least two clinical studies (20,21), enhanced granulation tissue formation has been observed using ROCF-V with saline instillation. This has been corroborated in one porcine study (38).

Following each dressing change, a wound reassessment should be performed to determine if additional wound therapy is needed to achieve the goals of cleansing and/or granulation. If the goal is not met, then further debridement and wound therapy should be considered until the goal is achieved. Upon goal achievement, the health care provider may decide to surgically close the wound or allow the wound to heal by secondary intention.

Case studies

The following case studies demonstrate the successful use of NPWTi-d.

Case study 1

Patient was a 78-year-old female with severe peripheral vascular disease, atrial fibrillation, diabetes and hypertension. She underwent a femoral artery to popliteal artery bypass and then needed an emergent thrombectomy of the dorsalis pedis artery. The transient critical ischaemia produced a 10×12 cm wound with exposed tendons (Figure 2A). An active wound bed preparation strategy was selected for delayed closure. The goal of granulation with the benefit of cleansing resulted in NPWTi-d selection. NPWTi-d consisted of instillation of 0·9% saline with a 10-minute dwell time, followed by 120 minutes of NPWT at −125 mmHg, continuously. The wound was treated for 9 days with NPWTi-d with dressing changes performed on days 2, 5 and 7 (Figure 2B). An STSG under local anaesthesia was performed because the patient suffered a recent myocardial infarction. Standard NPWT was applied to the STSG as a bolster for 3 days postoperatively. On postoperative day 14 (Figure 2C), the patient was weight bearing, dorsiflexing the ankle, and ambulating with no drainage or dressing required.

Case study 2

Patient was a 75-year-old male with scalp angiosarcoma and a failed latissimus dorsi secondary to embolic event, which left an 11×14 cm exposed skull devoid of periosteum (Figure 3A). An active wound bed preparation was selected for delayed closure. The goal of granulation with the benefit of cleansing resulted in NPWTi-d selection. NPWTi-d consisted of instillation of 0·9% saline with a 10-minute dwell time, followed by 120 minutes of NPWT at −125 mmHg, continuously. After 12 days of NPWTi-d, a skin substitute was applied (Figure 3B) with NPWT as a bolster postoperatively for 3 days. An STSG was applied 3 weeks later followed by NPWT as a bolster for 3 days. At 4 months postoperatively, the graft appeared well and tolerated radiation therapy (Figure 3C).

Case study 3

A 38-year-old otherwise healthy female was involved in a motor vehicle crash with gross contamination around an open ulnar bone fracture (Figure 4A). The goal of cleansing prompted NPWTi-d. NPWTi-d consisted of instillation of 0·9% saline with a 10-minute dwell time, followed by 120 minutes of NPWT at −125 mmHg, continuously. NPWTi-d was used for 6 days while multisystem injuries were stabilised. An STSG was applied (Figure 4B) with NPWT as a bolster for 3 days. Figure 4C shows good graft take at 14 days post STSG. At 6-month follow-up (Figure 4D and E), the patient continued to have an excellent range of motion.

Case study 4

A previously healthy 51-year-old male presented with necrotising fasciitis on the arm and torso (Figure 5A). On the day of presentation, the patient was taken to the OR for initial debridement and application of standard NPWT using silver foam (V.A.C. GranuFoam Silver™ Dressing) (Figure 5B). After 24 hours post presentation and second debridement (Figure 5C),

Table 4 Wound characteristics and strategy selection

Wound characteristics	Strategy	DFU	VLU	Dehisced surgical wounds	Burns	Traumatic	PU	Open amputation
Exudative	C	X	X	X		X	X	
Necrotic	C	X	X	X	X	X	X	
Tissue loss	G	X			X	X	X	
Infected	C	X	X	X	X	X	X	
Contaminated/colonised	C	X	X	X	X	X	X	
Tunnelling	G	X					X	
Desiccated	G				X			
Malodourous	C	X	X	X	X		X	
Stalled	C	X	X				X	
Hypoxic wound bed	G	X	X				X	
Oedematous	G	X	X	X		X	X	X
Pain	C		X	X	X	X	X	

C, cleanse; G, granulate; DFU, diabetic foot ulcer; VLU, venous leg ulcer; PU, pressure ulcer.

NPWTi-d was chosen as a goal of cleansing and consisted of instillation of 0·9% saline with a 10-minute dwell time, followed by 120 minutes of NPWT at −125 mmHg, continuously. The patient received NPWTi-d for 6 days with dressing changes on days 2 and 4 while systemic infection and organ failure was stabilised. On day 7, delayed primary closure was followed by STSG with NPWT as a bolster for 3 days (Figure 5D). At 18-week follow-up (Figure 5E and F), the patient had excellent range of motion.

Case study 5

A 46-year-old male presented with a large infected plantar (Figure 6A) and lateral malleolar ulcer with exposing structures (Figure 6B). Patient history included type 1 diabetes and neuropathy with no ischaemia (Ankle Brachial Index, ABPI 0·9). For initial treatment, the wound was debrided (Figure 6C) and standard NPWT (−125 mmHg, continuously) was applied for 3 weeks (Figure 6D). A dermal substitute was then applied (Figure 6E), followed by an STSG 2 weeks later (Figure 6F). However, 2 weeks post STSG, an infection developed (Figure 6G). The patient returned to the OR for second debridement, followed by initiation of NPWTi-d (Figure 6H), which consisted of instilling saline with a dwell time of 10 minutes followed by 4 hours of NPWT continuously. After 2 weeks of NPWTi-d initiation, the wound showed increased granulation tissue formation (Figure 6I). Another dermal substitute was applied (Figure 6J) followed by an STSG 2 weeks later. Wound healing had progressed at follow-up (Figure 6K).

NPWTi-d and the reconstructive ladder

The reconstructive ladder has functioned in its modern, conventional form for over 30 years (52). Its principles of progressively complex procedures to address wounds and other soft tissue defects remain accurate as closure continues to fall into the three realms of: (i) non-operative, topical wound healing (advanced secondary intention methods, including NPWT); (ii) direct closure (primary or secondary) and (iii) tissue transfer, which includes both non-vascularised (e.g. split-or full-thickness skin grafts, fat transfer, cartilage or bone grafts) and vascularised transfers (e.g. local tissue transfers and rearrangements, regional pedicled flaps, distant pedicled flaps or free tissue transfers).

The reconstructive ladder serves as a guide for different levels of interventions for an open wound. NPWT and now NPWTi-d change the way the ladder is used as it is easier to slide between 'rungs' of the ladder by changing the original defect during preparatory wound care (Figure 1). During strategy selection for wound treatment, the defect characteristics will change often allowing a less morbid procedure to be performed. This results in a more fluid reconstructive plan that is adjusted at every reassessment during NPWTi-d. NPWTi-d can also enhance closure and downstage some of the reconstruction techniques. Downstaging reconstructions with the use of NPWT has already been documented (53–55) but now with the addition of NPWTi-d, this can be performed in more of an efficient manner as the benefits of instillation are added. For example, NPWTi-d can be used to help prepare an abdominal wound with intact fascia (i.e. not an open abdominal wound) for delayed primary closure or to downstage a lower extremity wound with exposed bone from a possible free flap to a local tissue transfer.

In our setting, NPWTi-d may be proposed as a strategy for granulation tissue formation in extensively infected wounds with cavities and undermining or in wounds that are not readily responsive to standard NPWT. Other situations, such as the need for successive debridements in vascular-impaired wounds, may serve as potential uses for NPWTi-d. Currently, NPWTi-d is only available in acute-care facilities, such as hospitals. In some European countries, the same NPWTi-d system can be used for a limited period of time – less than 2 weeks – in post acute settings and mainly after a period of unproductive standard NPWT. The use of NPWTi-d in between two periods of NPWT is suggested in complex and recalcitrant wounds. Future studies are necessary to evaluate the use of NPWTi-d in other care settings.

Health economics

With the rising costs of health care, hospitals and other facilities are seeking better ways to identify and incorporate

Table 5 Topical wound solutions used with NPWTi-d as reported in the literature

Solution class	Solution	Author	Instillation therapy settings	Patient/wound type
Biguanides	Polyhexanide 0·01% (Prontosan)	Gabriel *et al.* (44)	Dwell time: 1–60 seconds NPWT time: 1 or 2 hours Dwell frequency: 12 or 24 times daily	9 patients with complex extremity or trunk wounds
		Kim *et al.* (22)	Dwell time: 6 or 20 minute NPWT time: 2 or 3·5 hours Dwell frequency: 8 or 12 times daily	68 patients with infected wounds
		Schintler *et al.* (61)	Dwell time: 20 minute	15 patients with infected soft tissue wounds
Isotonic Solutions	Normal saline (sodium chloride 0·9%)	Gabriel *et al.* (44)	Dwell time: 1–60 seconds NPWT time: 1 or 2 hours Dwell frequency: 12 or 24 times daily	39 patients with extremity or trunk wounds
		Brinkert *et al.* (20) and Fluieraru *et al.* (21)	Dwell time: 10 minute NPWT time: 4–12 hour Dwell frequency: 2–6 times daily	• 12 patients with complex wounds • 12 patients whose wound failed to progress after conventional NPWT • 131 patients with complex wounds (e.g. open fracture, pressure ulcer, diabetic foot ulcer and non-healing postoperative dehiscence wounds)
Hypochlorite-based solutions	Dakin's solution (quarter strength)	Raad *et al.* (2010) (62)	Dwell time: 10 minute NPWT: 50 minute Dwell frequency: 24 times daily	5 patients with colonised venous stasis ulcers
		Wolvos (46)	Dwell time: 5 minute NPWT: 4 hours Dwell frequency: 6 times daily	26-year-old female with abdominal wound with exposed biological mesh
Hypochlorous acid solutions	Microcyn	Wolvos (46)	Dwell time: 5–10 minute NPWT: 2–4 hours Dwell frequency: 6–12 times daily	5 patients with difficult-to-heal wounds: • postoperative contaminated wound at a previous ileostomy site • contaminated complex chest wall wound • infected hip wound • several surgeries for bowel perforation and abdomen washout • open infected transmetatarsal foot wound with osteomyelitis
Silver nitrate	Silver nitrate (0·5%)	Gabriel *et al.* (25)	Dwell time: 1 second NPWT: 2 hour Dwell frequency: 12 times daily	15 patients with complex open infected wounds

NPWT, negative pressure wound therapy.

cost-effective wound therapies without compromising patient care. The challenge emerges when attempting to balance the initial higher costs of advanced wound healing technologies with overall costs for wound care. Wounds are a major source of patient morbidity and cost and continue to stress the global health care system. Therefore, cost-effectiveness analyses have become a critical tool for administrators at health care facilities who are responsible for selecting new and existing wound healing therapies.

Previous studies have applied cost dollars to clinical outcomes in randomised controlled trials comparing NPWT with advanced moist wound healing. Results have shown both clinical and economic benefits of using NPWT (35,36,56,57). Other studies have also demonstrated cost savings with early initiation of NPWT compared with late initiation (58,59). More recent studies have now investigated the potential cost savings of NPWTi-d. A recent poster presentation by Alcantara *et al.* proposed that a protocol of debridement, NPWTi-d using a topical wound solution and a STSG with NPWT bolster has the potential to be economically advantageous and a more effective alternative to standard compression therapy for large, chronic venous leg ulcers (60). The findings from Kim *et al.* also demonstrated reduction in OR debridements and length of hospital stay with NPWTi-d compared with NPWT that potentially can be translated into cost savings (22). In a retrospective study by Gabriel *et al.* (44), patients with extremity or trunk wounds received either NPWT or NPWTi-d using saline or polyhexanide. NPWTi-d patients averaged fewer trips to the OR for debridements and fewer days of therapy compared with NPWT patients. Applying cost dollars to a hypothetical model based on these clinical outcomes, NPWTi-d showed better cost savings than NPWT (44). Further prospective controlled studies are necessary to determine the comparative cost-effectiveness of NPWTi-d with other advanced wound therapies.

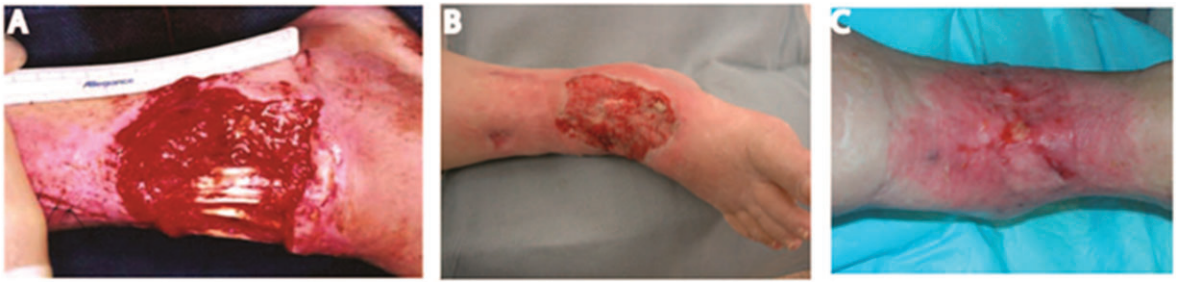

Figure 2 (A) Initial presentation of wound: goal of granulation with benefit of cleansing. (B) Wound after 9 days of NPWTi-d (saline instillation with a 10-minute dwell time, followed by 120 minutes of negative pressure wound therapy). (C) Wound 14 days postoperative split-thickness skin graft (STSG).

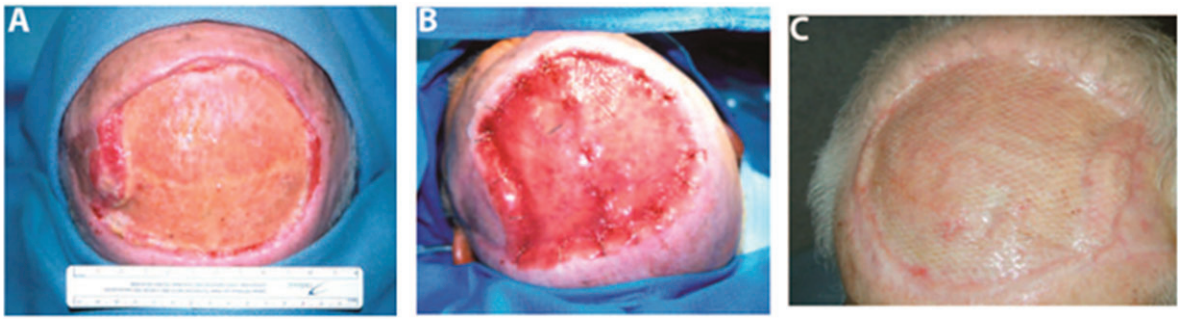

Figure 3 (A) Initial presentation of wound; goal of granulation with benefit of cleansing. (B) Application of skin substitute. (C) Graft at 4-month follow-up.

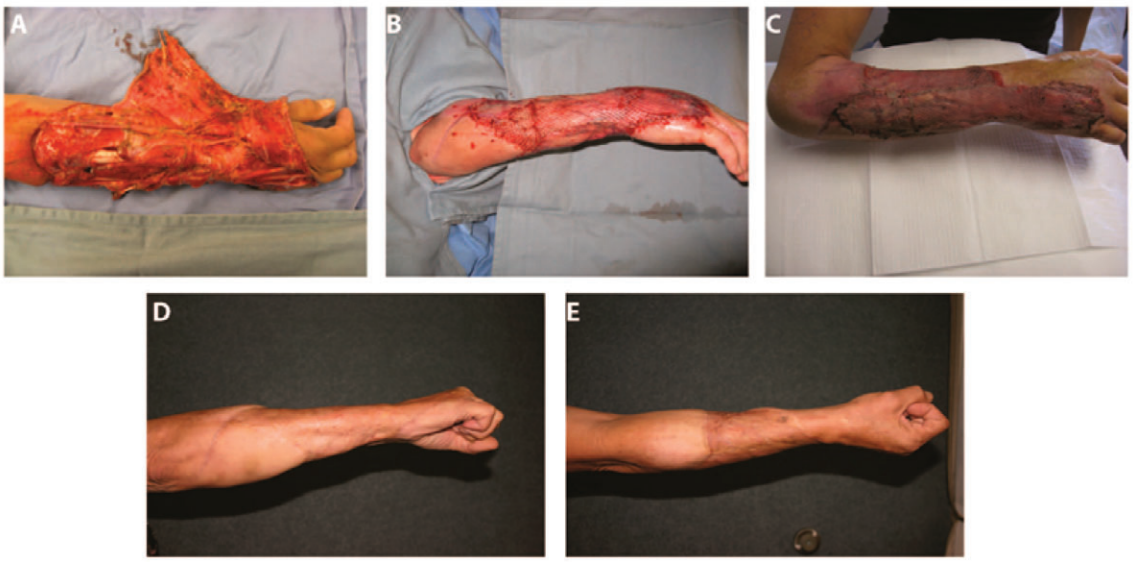

Figure 4 (A) Initial presentation of wound; goal of cleansing. (B) Application of split-thickness skin graft (STSG). (C) Post STSG day 14. (D) Follow up at 6 months. (E) Follow up at 6 months.

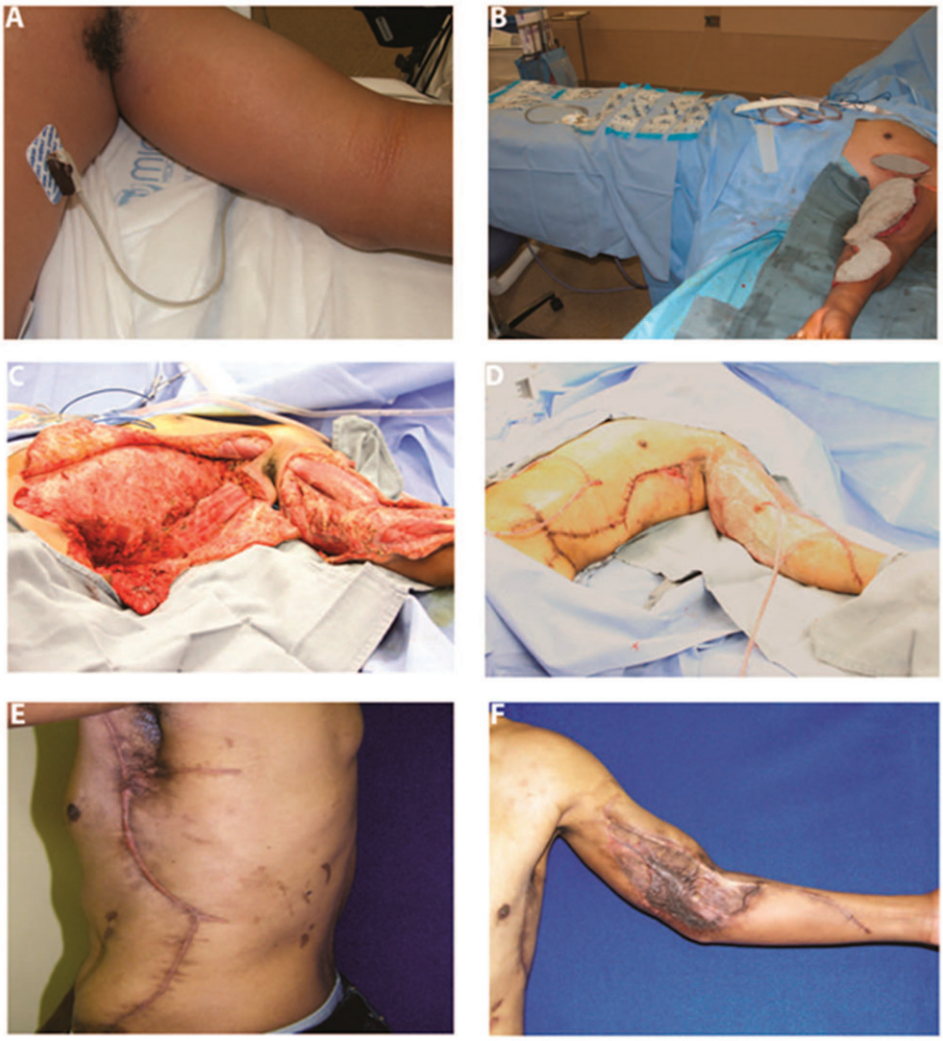

Figure 5 (A) Initial presentation of patient. (B) Day of presentation post debridement with traditional negative pressure wound therapy (NPWT) using silver dressing. (C) After 24 hours post presentation and second debridement; primary goal of cleansing. (D) After 6 days of NPWTi-d (saline instillation with a 10-minute dwell time, followed by 120 minutes of negative pressure wound therapy), wound was surgically closed and split-thickness skin graft (STSG) was applied to arm. (E) Torso at 18 weeks follow-up. (F) Arm at 18 weeks follow-up.

The key comparator for NPWTi-d in this economic environment should be immediate debridement and closure. However, at present, it is acknowledged that debridement alone in critically colonised and infected wounds does not adequately reduce bioburden. Therefore, immediate closure and/or grafting in these patients may have poor outcomes. NPWTi-d also appears to fit best in the reconstructive ladder in these exact wounds, serving primarily as an acute preparation for planned delayed primary closure at a fixed endpoint of therapy, or as a 'jump start' strategy that uses NPWTi-d for 1 week to stimulate a wound that is not responsive to standard NPWT.

Discussion

While NPWTi-d clearly has a role to play in helping the clinician prepare the wound bed for closure, when to exactly use the device seems to be the primary question. As the data have outlined, the strengths of NPWTi-d are: demonstrable reductions in bioburden (over traditional therapy and over NPWT), enhanced depth of granulation bed and fewer OR trips for debridement. Therefore, it would appear that a logical place to use NPWTi-d would be on wounds that require these attributes, including wounds that are larger (greater than 40 cm^2) or deeper, have high bacterial burdens or complex diabetic foot wounds.

Areas of opportunity for expanded NPWTi-d use include outside the acute-care hospital setting as well as the appropriate positioning in the wound care continuum. The wound dressing change also requires greater attention to periwound maceration. Currently, we have a limited understanding of the applicability of the various topical wound solutions, which need to be better delineated. Finally, the ideal dwell time likely depends on the goals of therapy and the topical wound solution chosen. At present, dwell times have been somewhat arbitrary and the choice of topical wound solution has been driven by local, regional and in some cases national preferences.

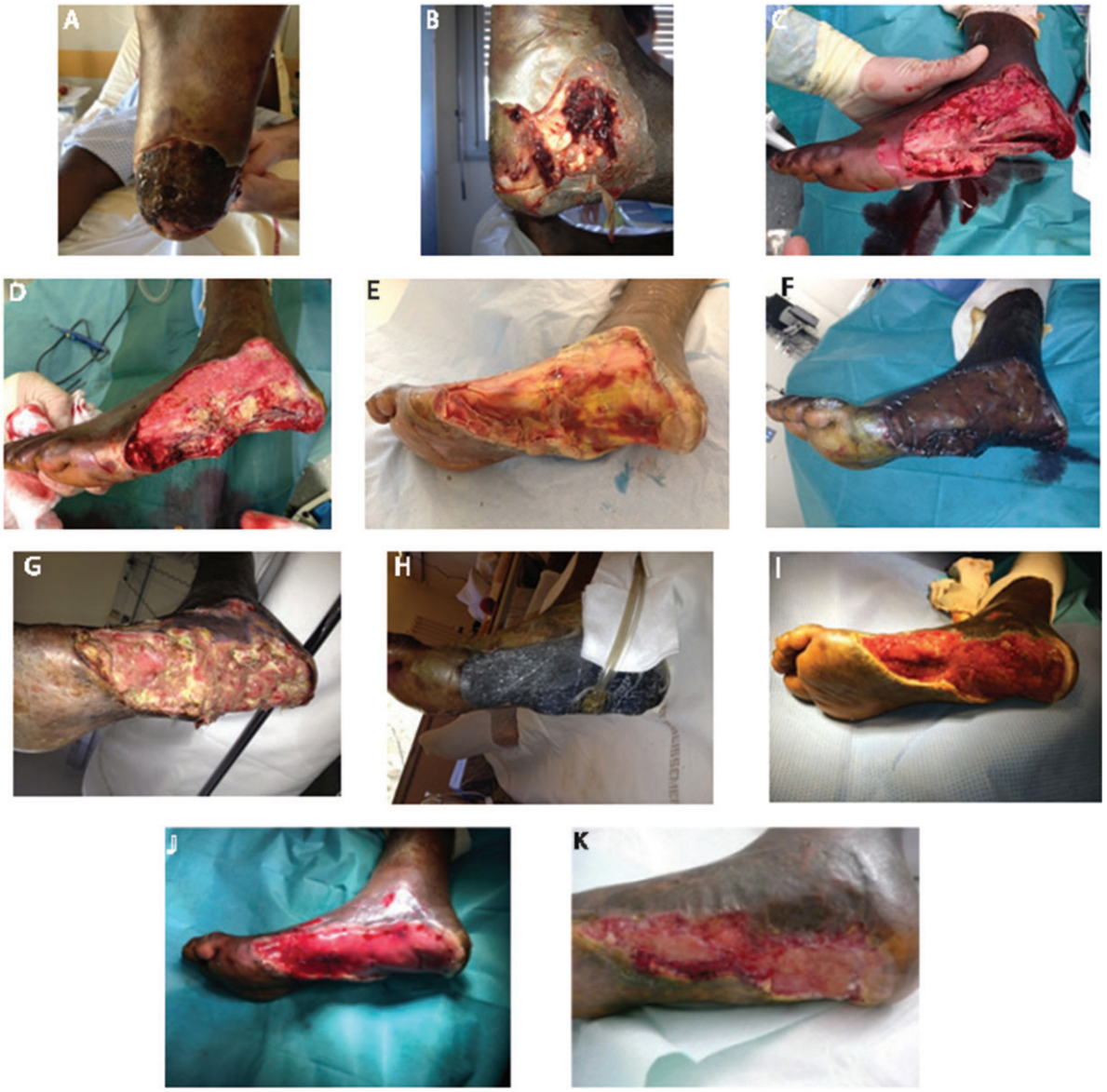

Figure 6 (A) Initial presentation of plantar wound. (B) Initial presentation of lateral malleolar wound. (C) Initial debridement. (D) After 3 weeks of standard negative pressure wound therapy (NPWT). (E) Application of dermal substitute. (F) Application of split-thickness skin graft (STSG). (G) Development of infection. (H) Application of NPWTi-d (saline instillation with a 10-minute dwell time, followed by 4 hours of negative pressure wound therapy). (I) Wound after 2 weeks of NPWTi-d. (J) Application of dermal substitute. (K) Wound at follow-up.

At present, the reported clinical benefits make NPWTi-d a potentially economic adjunctive method of managing the large complex and/or infected wound in the inpatient setting. These factors combined with the robust granulation tissue generated by NPWTi-d may allow for a re-investigation of NPWTi-d as a management strategy for wounds where it has not shown as much benefit as one would expect (e.g. pressure ulcers).

Conclusions

As clinicians, our goal is to provide the best treatment approach for wounds. As outlined in this review, the addition of instillation can improve the overall outcome if initiated in a timely fashion. Although there is currently no level 1 or 2 evidence, the recently published articles can serve as an example of how aggressively some of the wounds can be managed with addition of instillation. We have seen a more aggressive approach to wound closure instead of watching the wound granulate over weeks to months. There is also a paradigm shift such that the wound will no longer need to be packed or treated with NPWT indefinitely. Now with the addition of instillation, the wound can be prepared for closure in an efficient manner, which may lead to minimising the length of stay and overall health care costs.

At present, the role for NPWTi-d appears to be in the larger infected wound that is best served by acute-care hospitalisation with a rapid jump to closure. Many of these wound types, such as venous leg ulcers greater than 40 cm^2, pressure ulcer

with a greater duration than 3 months and bony foot resections for acute infection, are poorly studied in part because of their poor outcomes. Therefore, a grouping of large case series looking at these wound types or possibly a large prospective registry evaluating the therapy with real-world topical wound solutions versus immediate debridement and closure would be the most logical next step in further exploring the benefits of this promising therapy.

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