Evidence-based recommendations for negative pressure wound therapy: Treatment variables (pressure levels, wound filler and contact layer) — Steps towards an international consensus

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Introduction

Negative pressure wound therapy (NPWT) is a treatment modality that has become widely adopted for a broad range of wound indications since its advent over 15 years ago. NPWT is a generic technology, which can deliver a broad range of treatment goals. It can be delivered to a wound using a range of variables including the negative pressure level, wound filler and wound contact layer (WCL). Choosing between these variables may affect the achievement of the required treatment goals, yet the evidence to inform these choices is hidden within a multitude of clinical studies and has not been specifically reviewed to date. The aim of this review was to condense the existing body of literature on NPWT treatment variables into evidence-based clinical recommendations and to provide guidance to clinicians to decide which NPWT variables may be most appropriate in specific clinical scenarios. Although
Evidence-based recommendations for negative pressure wound therapy

Methods

To provide an unbiased review of the NPWT literature, a systematic review of peer-reviewed articles was undertaken in the following manner. The National Library of Medicine (NLM) PubMed database was searched (August 2010) using the search terms ‘NPWT OR negative pressure wound therapy OR vacuum-assisted closure OR topical negative pressure’. No filters were applied. A total of 1064 records were retrieved ranging from October 1996 to August 2010. Searches were limited to studies published after 1996 (when modern formats of NPWT became commercially available). The 1064 records were examined to identify all studies investigating the effect of different pressure levels, different wound fillers and WCLs and the effect of NPWT on microbiology. Articles were reviewed with respect to the following rejection criteria: not on NPWT (45); veterinary treatment (four); reviews/comments (260); off-label (non-licensed) indications, such as exposed organs (183); no abstract available (120); article not in English (54); and clinical studies reporting fewer than 10 patients (185), leaving a total of 213 full articles to obtain and review. Those articles containing relevant end points were reviewed further and were used to develop and support the recommendations.

Articles were also divided by indication to aid indication-specific discussion points. For this purpose, studies were not limited by patient numbers.

The main search was supplemented, where appropriate, by literature identified by other means. Where studies of particular relevance were identified in a language other than English, every effort was made to obtain translation and English abstracts were reviewed, where available. All relevant studies were reviewed, regardless of the type of study or method of delivery of NPWT being reported.

Development of recommendations

The recommendations described in this report were determined during a series of meetings between the members of the NPWT expert panel. Recommendations were developed according to a modification of the Scottish Intercollegiate Guidelines Network (SIGN) classification system. Table 1 describes the classification of the levels of evidence used and the corresponding strength of recommendation that can be made from each evidence level. Evidence levels were identified in the text as outlined in Table 1(b) and referred to as Level (L) 1–4, as appropriate. The SIGN guidelines were modified by using specific terminology to clarify the strength of each evidence-based recommendation (‘Must’ for Grade A, ‘Should’ for Grade B and ‘May’ for Grade C).

Formal consensus development

During the development phase, consensus was obtained between the expert panel members. At this stage, the recommendations were modified until 100% agreement was obtained.

Treatment goals

The mechanism of action of NPWT is known to be multimodal. The multimodal effects of NPWT can deliver a broad range of treatment goals associated with various aspects of the NPWT mode of action (MoA) (Table 2):

Managing and protecting the wound

The ability of NPWT to protect the wound depends on the physical ability of NPWT to provide an airtight barrier between the wound and the external environment as a result of the integral adhesive drape. This provides a dual function; the drape maintains a moist wound environment, conducive to wound healing, as well as providing a barrier to external insult (e.g., contamination by particulates or microbes). The removable nature of the NPWT dressing confers a temporary nature upon it.

To prepare the wound for surgical closure/to progress the wound by secondary intention

NPWT can reduce the size and complexity of the wound in two main ways. First, upon application of negative pressure, the wound immediately contracts (macro-deformation). Second, over several days, NPWT also reduces the size of the wound through the formation of granulation tissue, which may be beneficial for surgical closure and especially for closure by secondary intention. A granulating bed can improve the suitability of the wound bed (e.g., by covering exposed structures, such as tendon or bone) for closure by either flap or graft (L3). In some circumstances, a wound with a large defect may be encouraged to in-fill completely through the generation of granulation tissue induced via NPWT, so that more complex reconstructive procedures (e.g., free flaps) are no
longer required and simpler procedures such as a split-thickness skin grafting (STSG) can be used instead (L2-10,11; (L3).6,12 The way in which NPWT promotes granulation tissue formation is in itself multimodal and complex. Application of NPWT wound fillers to the wound bed causes microscopic deformations in the wound bed (microdeformation), which are thought to contribute to granulation tissue formation (L3).17 In addition, changes in blood flow in the immediate vicinity of the wound may also contribute to granulation tissue formation. (L3).18–22 NPWT can also reduce oedema, which may contribute towards improved tissue perfusion.

To improve outcomes after STSG

NPWT may be able to improve the outcome of a graft procedure by providing a bolstering effect. Application of NPWT over an STSG can result in a reduced incidence of graft failure or re-graft procedures compared with standard bolster techniques (L3).23–25 (L1)26–28; (L2). NPWT can deliver all the advantages of a bolster dressing in addition to other advantages, such as active fluid removal, which further contributes to reduced seroma formation (L3).29,30 This wound-stabilisation effect can help to mobilise the patient in some scenarios.

To improve patient comfort

Wound exudate is well managed by NPWT, as it is diverted and contained within the canister. This not only protects the wound edges and surrounding skin from maceration but also reduces the frequency of dressing changes, compared with conventional dressings (L3). This leads to reduced pain for the patient as well as reduced frequency of exposure of the wound to the external environment. Earlier patient mobilisation also contributes towards a sense of patient well-being, such as in skin grafts treated with NPWT (L3).

To reduce costs

The use of NPWT has been shown to reduce costs compared with conventional wound therapy. This can be achieved through a combination of improved outcomes and reduced use of nursing resources (as a result of fewer dressing changes) and has been demonstrated in a number of Level 1 studies. Despite the higher cost of an NPWT dressing compared with conventional wound care, these improved outcomes make the therapy more cost-effective. Early use of NPWT in trauma patients has been claimed to reduce overall costs compared with a delayed introduction of NPWT.
Treatment goals, the related MoA and the timing

To achieve each of the above treatment goals, slightly different aspects of the overall MoA are involved. It follows that, in some wounds where certain goals are most important, only the MoAs which relate to that goal are relevant. One example is the application of NPWT over an STSG, where the primary goal is to bolster the STSG with the desired clinical outcome of reduced risk of graft failure. In this scenario, a goal, such as granulation tissue formation, is not as relevant. Management of excess fluid, however, may be highly relevant as a secondary goal in achieving the expected improved clinical outcomes.

Although some of the clinical outcomes that can be achieved through the use of NPWT may be equally important, many clinicians find that it is advantageous for a single goal to be chosen as the primary goal. Achievement of this goal within a predetermined time frame drives a reassessment of the needs of the wound and patient in terms of subsequent therapy. This may involve surgical procedures or other advanced wound dressings. This re-evaluation is necessary to avoid overuse of NPWT past the point where the therapy is of particular benefit.

How the identification of treatment goals impacts on choice of treatment variables

The definition of which treatment goal and which aspects of the MoA are most important in an individuals’ wound therapy can have a significant impact on the choices made during application of therapy. For example, different goals may be best delivered with the choice of a particular pressure setting or wound-filler material. The following sections seek to describe the impact of these options by reviewing the published evidence base as a platform to support evidence-based recommendations.

Evidence-based recommendations

Choice of WCL and filler material

In recent years, a number of options for the provision of NPWT have become available. These include a variety of WCL materials (including the option of not including a WCL) and different wound-filler materials (principally polyurethane (PU) ‘black’ foam, polyvinylalcohol (PVA) ‘white’ foam and anti-microbial-impregnated medical gauze. In order to have a proper nomenclature for future discussion we propose the term “tissue interface” to describe the point at which either the wound filler or a wound contact layer (WCL) meets the tissue since the nature of this interface may determine the tissue surface response to NPWT.

Definitions

Wound filler — The material, usually supplied as part of a dressing kit, used to fill the wound. This is most commonly composed of either black polyurethane (PU) foam or gauze. This can be directly applied to the wound bed or used in conjunction with a WCL. Wound contact layer (WCL) — A non-adherent layer sometimes applied directly onto the wound bed and beneath the wound filler. Tissue interface — The point of interaction between the tissue and the material delivering negative pressure; this will be either the surface of the wound filler or the WCL, if such is used.
Which Wound-filler material?

The vast majority of published evidence relates to PU foam, also commonly referred to as ‘black foam’. The next largest body of evidence relates to the use of anti-microbial gauze as filler for NPWT. There is a growing body of in vivo evidence, which demonstrates that several aspects of the MoA of NPWT are achieved, regardless of the choice of wound filler. No differences in the degree of blood flow or wound contraction in small wounds have been observed with either foam or gauze, although PU foam results in more contraction than gauze in large wounds. Microdeformation of the wound bed also occurs beneath both PU foam and gauze, although foam may induce a higher level of strain than gauze. PU foam and gauze have been proven to equally transmit pressure to the wound bed.

Furthermore, acute wounds treated with foam- or gauze-based NPWT were prepared for skin grafting in a similar period of time (25.9 and 24.7 days, respectively), while equivalence between these two wound fillers cannot yet be claimed (due to the relatively small sample sizes and possible low sensitivity of the randomised trials). There appears no reason to doubt that foam- and gauze-based NPWT are both capable of delivering clinically relevant effects. Thus, the choice of which filler to use may be at least partially dependent on practical considerations, such as ease of application, effects on patient experience, availability and cost.

Gauze ‘should’ be considered (Grade B) and PVA foam ‘possibly’ considered (Grade D) to reduce pain on dressing removal (Table 3).

In a randomised trial comparing PU-foam- and gauze-based NPWT, pain on dressing removal experienced by the gauze-treated patients was significantly less than in foam-treated patients. These observations are supported by numerous anecdotal reports. It is thought to be due to the lower level of tissue ingrowth observed in gauze compared with foam, which has been demonstrated in vivo (L3). Removal of the foam along with the ingrown tissue causes tissue damage and bleeding, as well as being painful for the patient. The level of tissue damage caused by removal of gauze-based NPWT was reported in a non-comparative series of 152 patients. Ninety eight percent of patients received no damage to the wound, following removal of the gauze NPWT filler.

Alternative ways of reducing the pain experienced during the removal of PU-foam-based NPWT include instillation of a topical lidocaine into the wound prior to dressing removal, instillation of the wound with warm saline prior to dressing removal, more frequent dressing changes to avoid tissue ingrowth or the use of a WCL (discussed in more detail in the following section). Adoption of any of these strategies might complicate the NPWT dressing application compared with the simpler strategy of changing the wound-filler material and even reduce the benefit.

Pain can also be experienced during application of pressure. It is believed that the greater the degree of contraction, the greater the degree of wound pain. As discussed earlier, gauze has been shown to induce less contraction in large wounds compared with PU foam. In wounds where significant pain on application of pressure may be expected, it may be advantageous to apply a gauze-based filler as opposed to a PU-foam filler.

Use of PU-foam wound filler is recommended where a rapid surface granulation response is desired (Grade D); Table 3.

Formation of granulation tissue is a key MoA of NPWT. It contributes to closure by secondary intention and provides a good wound bed suitable for surgical closure. Several commentators have observed that PU foam promotes rapid and thick granulation tissue. Conversely, PVA foam and gauze are thought to form thinner but more stable...

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**Table 3** Recommendations relating to wound filler material and WCL.

<table>
<thead>
<tr>
<th>Treatment goal or variable</th>
<th>Recommendation and Grade (A–D)</th>
<th>Reference (Evidence Level, 1–4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>When to use different wound filler materials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain on dressing removal</td>
<td><strong>Gauze should</strong> be considered to reduce pain on dressing removal</td>
<td>B L1-43, L3-46, 47, 48, 49, 51.</td>
</tr>
<tr>
<td></td>
<td>Possibly consider PVA foam to reduce pain on dressing removal</td>
<td>D L3-53, L4-52</td>
</tr>
<tr>
<td>Granulation tissue formation</td>
<td>Use of PU foam wound filler is recommended where a rapid surface granulation response is desired</td>
<td>D L3-124, L4-55</td>
</tr>
<tr>
<td>Wound dimensions/Shape/Contour</td>
<td>It is possible to use foam for deep uniform contractible wounds and gauze for shallow non-contracting wounds or complex deep cavities</td>
<td>D L1-43, L3-21, 41, 46, 51, 58.</td>
</tr>
<tr>
<td>When to use wound contact layers (WCL)</td>
<td>Use of a non-adherent WCL is recommended when using PU-foam-based NPWT to bolster a skin graft</td>
<td>D L3-31</td>
</tr>
</tbody>
</table>
granulation tissue and, in cases where rapid and thick granulation is not wanted gauze or PVA foam can be the preferred wound-filler material.34

It is hypothesised that thinner granulation tissue may lead to less fibrosis and scarring. Fraccalvieri et al. (2011)65 (L3) treated wounds with either PU-foam- or gauze-based NPWT prior to STSG and used ultrasound to measure the depth of scar tissue several months after grafting. Foam-treated wounds had median depth of 20 mm of scar tissue compared with 7 mm in gauze-treated wounds. The patient numbers in this study are low, and a larger study cohort would be of interest.

It is possible to use foam for deep uniform contractible wounds and gauze for shallow non-contracting wounds or complex deep cavities Grade D; Table 3.

PU foam is well suited to large, deep, uniformly shaped wounds with few contours or tunnels46 (L3). These wounds require minimal pre-shaping of the foam. No difference in wound contraction in small wounds has been observed with the use of PU foam or gauze39,40 (L3), although foam results in more contraction than gauze in large wounds34 (L3). Foam may therefore be of benefit in deep, uniform wounds, which will benefit from a higher level of wound contraction and stabilisation, for example, fasciotomy wounds. These are deep and uniform wounds created by primary surgical incision to relieve compartment pressure, usually in the limb. NPWT can be applied as a wound dressing, while the cause of compartment pressure is relieved. More fasciotomy wounds treated with foam-based NPWT can be closed by suturing of the original incision compared with wounds treated by conventional methods (saline gauze alone), where a significantly greater proportion of wounds are repaired by STSG56,57 (L2). The ability of foam to contract to a greater extent than gauze in wounds of this size and nature may cause the edges of the incision to draw closer together, making PU foam the best candidate to apply in these and similar wounds.

Because of the lack of shape memory, gauze may contour better to the surface of complex-shaped wounds (Table 3)46 (L3) and is easy to apply51,58 (L3). Large, irregular wounds cavities and tunnels require extensive pre-shaping of PU foam, which can be very time consuming. In comparison, gauze is much more malleable than PU foam and can be applied with relative ease. Other consensus groups have suggested the use of PVA foam to awkwardly shaped wounds52 (L4). Although this material also needs to be pre-shaped, its shape memory is less than that of PU foam and may contour more easily to uneven surfaces compared with PU foam.

In shallow wounds, foam- or gauze-based NPWT can be chosen. Examples of shallow wounds include STSGs, and leg ulcers. It is well accepted that application of NPWT as a bolster for STSG is an effective means of increasing the percentage graft take or reducing the number of re-graft procedures required23–25 (L1)56–58; (L2). Although the majority of these studies were carried out using PU-foam-based NPWT with a WCL, evidence is emerging that similar clinical effects may be observed with gauze-based NPWT44 (L1),56,59 (L3). Hu et al. (2009)44 reported a randomised trial comparing a gauze-based and a foam-based NPWT. In one sub-analysis where NPWT was used to bolster STSG, they reported no difference in the survival rate of grafts (98% in both groups). Assuming indistinguishable clinical efficacy, the choice of wound filler for bolstering an STSG may depend on factors, such as ease of application.

When to use a WCL?

A WCL is a thin layer of material between the wound bed (and sometimes the surrounding skin) and the NPWT wound filler. The most commonly used WCLs are petroleum, paraffin or Vaseline-embedded gauze, silicone WCLs and low-density polyethylene. The main reasons for using a WCL include: to minimise tissue ingrowth into the wound-filler material and thereby to protect the wound bed from damage upon removal of the wound filler; to protect the patient from pain upon removal of the wound filler; and to achieve a specific effect on the wound bed by the use of an active WCL.

Recommendation: Use of a non-adherent WCL is recommended when using PU-foam-based NPWT to bolster a skin graft (Grade D) (Table 3).

A specific clinical indication where use of a WCL may be recommended is when foam-based NPWT is used to bolster a graft. This serves to minimise any disruption of the graft during dressing removal, thus encouraging a high rate of graft take. The insertion of a WCL between the graft and the foam is widely reported23–26 (L1).

Blackburn et al.31 (L3) suggested that WCLs which allow fluid transit are preferred and, hence, Vaseline-embedded gauzes may not be ideal. However, other authors have considered that paraffin gauze has been shown not to disrupt the transmission of pressure to the wound bed and may be a good candidate WCL39 (L3).

Use of a less adherent filler, such as gauze58,59 (L3) or white PVA foam7 (L2) in the bolstering of STSG to the wound, may remove the need for an additional WCL, as these wound filler materials are essentially non-adherent to the wound.

Use of a WCL is also reported to be of benefit during application of NPWT into a wound where rapid granulation tissue formation is expected and a high degree of wound contraction is required53–56 (L4). This is a strategy adopted by many clinicians faced with non-compliant patients because of the pain experienced during dressing changes. PU foam, in particular, is subject to ingrowth of new granulation tissue into the interstices, and this can cause adherence of the foam to the wound bed and result in difficulty, damage and pain during removal of the foam63 (L1),69 (L3). In such wounds, placement of a WCL between the surface of the foam and the wound bed minimises tissue ingrowth and may reduce pain and tissue damage on dressing removal.53

A WCL may also be used because of the specific advantages it may confer on a wound. For example, in a wound at risk of infection, an anti-microbial material may be used as a WCL. The use of NPWT in infected wounds is discussed in more detail in a later section.

Whatever the reason for the use of a WCL, it should always be considered that placement of any WCL between the wound bed and the wound filler may reduce the pressure delivered to the wound bed.60,61 Further, any beneficial effect of NPWT obtained through microdeformation,17 which depends on direct contact of the wound filler with the wound bed, is obstructed by the use of a WCL. One other consensus
document suggests that a WCL should never be inserted underneath the wound filler, for this reason.69

Note that a special contact layer must be used to prevent granulation tissue formation on exposed bowel during NPWT for an open abdomen. This topic will be the subject of a future communication.

**Choice of pressure level**

Upon the adoption of commercial NPWT, a standard pressure setting of −125 mmHg became the accepted norm even though the original clinical description recommended lower pressures on some wound types.54 The original basis for the −125-mmHg pressure setting was based on optimal blood-flow changes observed in a porcine excisional wound study, as reported by Morykwas et al., 1997 (L3).62 Granulation tissue formation was seen to be significantly increased at −125 mmHg compared with no pressure. A later study assessed the granulation tissue formation at the pressure settings of −25, −125 and −500 mmHg63 (L3). No effects were seen at −25 mmHg compared with no negative pressure. When the negative pressure was raised to −500 mmHg, detrimental effects on granulation tissue formation were observed. Having identified the ineffective lower and upper ends of the pressure range (−25 and −500 mmHg), the remaining pressure level (−125 mmHg) was concluded as the optimal negative pressure, and this drove adoption as the pressure setting of choice in earlier clinical protocols. A more scientifically rigorous conclusion from this study is that the optimal pressure or a therapeutic range of pressures exists somewhere between −25 and −500 mmHg.

An additional aspect of pressure setting is the choice between continuous and intermittent delivery of pressure. This modality involves the cyclical release and reaplication of pressure, typically for 5 min on and 2 min off. Although some animal studies have demonstrated that the formation of granulation tissue is faster when intermittent pressure is applied62,64 (L3), this has yet to be rigorously explored in a clinical study. In the early clinical studies of NPWT, after a period of 48 h at constant negative pressure, the therapy would switch to a 5-min on, 2-min off intermittent regime24,65–67 (L3). Notwithstanding the stimulation of granulation tissue effect, there were two practical problems that were quickly identified. First, if the patients felt pain during the application of NPWT, then this was experienced at every cycle. Second, during the off period, if the wound had large volumes of exudate, there was a tendency for this to leak out and break the adhesive film seal. Consequently, intermittent therapy, particularly with foam dressings is less popular than it used to be. Borgquist et al. (2010)68 have shown in pig models that a “variable” therapy that provides smooth cycling between two different levels of negative pressure (‘high’ −80 mmHg and ‘low’ −10 mmHg), maintains the negative pressure environment throughout the therapy. Variable therapy was almost as effective as a fully on–off intermittent regime and might well be preferable to patients.

Use of intermittent or variable pressure when NPWT is used to bolster an STSG or in other wound types where maintenance of wound stability is important (e.g., to avoid wound dehiscence) is counterintuitive. This is discussed in more detail in an associated series of recommendations.4

The following section assumes the adoption of continuous negative pressure and aims to provide evidence-based recommendations to identify a therapeutic pressure range and to highlight clinical scenarios where changing the level of negative pressure settings within this range may be beneficial.

It is recommended that NPWT be used within a therapeutic range of −40 mmHg to −150 mmHg. Grade D; Figure 1; Table 4.

In recent years, clinicians have often found it necessary for a variety of reasons to modify the pressure settings, by switching to lower or higher ranges of pressures.69 This has lead to an interest in understanding the impact of varying the level of pressure on the MoA of NPWT and ultimately on clinical outcomes. As more research is published, much of it on in vivo experimental models, it is increasingly apparent that there may not be one single optimal level of pressure but an effective therapeutic range of negative pressure levels between −40 and −150 mmHg. Within this range, various aspects of the MoA of NPWT are effective, and different treatment goals may be achieved. Figure 1 summarises the evidence on the use of different pressures in NPWT.

Several in vivo studies suggest that pressures at the low to middle of this range (−40 to −80 mmHg) are often sufficient to result in changes in wound contraction in both small39,40 (L3) and large68 (L3) wounds. Increasing the level of negative pressure past this point resulted in minor further changes in wound contraction. In vivo studies have also consistently demonstrated increased blood flow at pressures ranging from −50 to −175 mmHg18–21,69,70,120 (L3). There is conflicting evidence demonstrating that negative pressure levels lower than −50 mmHg are effective in changing blood flow; some studies have identified blood-flow changes as low as −20 mmHg.69 Others observed no detectable changes in blood flow, at −25 mmHg69 and −37 mmHg.12 This variability may be due to differences in sensitivity of the different methods used. No studies to date have investigated the clinical effect of pressures as low as −20 mmHg on wound healing. However, several commentators have suggested that maximal blood-flow changes are observed at around −80 mmHg with only small incremental changes at higher negative pressures32,67 (L3).

Microdeformation of the wound surface was also observed to occur equally under pressures of −75 and −125 mmHg60 (L3). The effect of varying levels of pressure on the formation of granulation tissue has been reported in two animal studies62,63 (L3), as discussed above, and in one clinical study71 (L3). In a retrospective case series, McCord et al. (2007)71 applied different levels of negative pressure ranging from −50 to −125 mmHg to a variety of wounds in

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**FOOTNOTE:** Higher levels of negative pressure are here considered as those greater than −80 mmHg (−80 to −175 mmHg). Lower levels of negative pressure are those less than −80 mmHg (−40 to −80 mmHg). Pressures below −40 mmHg have been shown to deliver minimal benefit.18,69 Pressures greater than −200 mmHg may be detrimental to wound healing and may be undesirable due to increased patient pain experienced at this level.120,72
68 children from neonates to 18 years. No correlation was observed between the rate of granulation tissue formation and the pressure level, and good outcomes were largely observed.

This evidence indicates that application of negative pressure in the low to middle end of the therapeutic scale is required to induce maximal wound contraction, blood-flow changes, microdeformation and granulation tissue formation. It appears that the level of negative pressure may be varied, within the recommended therapeutic range, according to clinical circumstances, some of which are outlined below, without compromising on the MoA of NPWT clinical outcomes and treatment goals.

**Recommendation:** To reduce pain, lower negative pressures ‘may’ be considered (Grade C) (Table 4).

In patients or wounds sensitive to pain, the pain experienced during the initial application of NPWT can be very difficult to manage. The higher the level of negative

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**Table 4** Pressure related recommendations.

<table>
<thead>
<tr>
<th>Treatment goal or variable</th>
<th>Recommendation and Grade (A–D)</th>
<th>Reference (Evidence Level, 1–4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic Range</td>
<td>It is recommended that NPWT is used within a therapeutic range of –50 mmHg to –150 mmHg.</td>
<td>D L3 - 18, 19, 21, 22, 39, 40, 62, 63, 68, 69, 70, 71, 85.</td>
</tr>
<tr>
<td>To reduce pain</td>
<td>To reduce pain lower negative pressures may be considered</td>
<td>C L1 - 20&lt;sup&gt;a&lt;/sup&gt; L3: 71, 73–75.</td>
</tr>
<tr>
<td>Caution in ischaemic wounds</td>
<td>Avoidance of higher levels of negative pressure is recommended in wounds with compromised vascularity or otherwise at risk of ischaemia</td>
<td>D L3 : 21, 22, 75, 84</td>
</tr>
<tr>
<td>Fluid management</td>
<td>To manage high levels of wound exudate or wound fluid, higher levels of negative pressure is recommended</td>
<td>D L3: 85</td>
</tr>
</tbody>
</table>

<sup>a</sup> extrapolated data.
pressure, the greater the discomfort experienced by the patient (L1). In patients with low tolerance to pain, it may be advisable to initiate therapy at a lower level of pressure to avoid excessive pain (L3) and encourage compliance with therapy (L3). To alleviate the pain experienced by patients during therapy, it is common either to administer pain relief prior to application of the system or to reduce the pressure applied. In a more rigorous scientific study of pain on human-volunteer intact skin, it was observed that there was a positive correlation between pain and the level of negative pressure, with increasing pain experienced between –25 and –500 mmHg in PU foam (L1). It is therefore conceivable that application of negative pressure at the lower end of the therapeutic range may alleviate the pain associated with dressing application, while not compromising the clinical efficacy of the therapy.

Recommendation: Avoidance of higher levels of negative pressure is recommended in wounds with compromised/reduced vascularity or otherwise at risk of ischaemia (Grade D) (Table 4).

In tissue with compromised vascularity or perfusion, such as compromised flaps, some diabetic foot ulcers, arterial ulcers and burns, caution is recommended in applying high levels of negative pressure. Application of NPWT reduces blood flow in the immediate vicinity of the wound, and this effect becomes more pronounced with increasing negative pressure (L3). Other studies on intact volunteer skin have reported decreased blood flow as a result of application of NPWT. These studies raise concern that application of higher levels of negative pressure may exacerbate an existing ischaemia. However, it is important to balance the risk of creating a small, localised reduction in blood flow with the positive benefit of removing an existing oedema — this may be of particular relevance in burns where there is evidence that reduction of oedema mediated by NPWT may contribute to prevention of burn-wound progression (L2). The reluctance to increase the level of negative pressure in this early study stemmed from the positive correlation with conventional wound care alone (L3), demonstrating the importance of this step of the clinical pathway.

Role of NPWT as an adjunct to infection management

Infection is a well-recognised barrier to wound healing, a significant complication in the post-surgical wound and can result in patient morbidity and mortality as well as having significant economic implications. Regulatory bodies recommend careful consideration before NPWT is applied to an infected wound, and the use of NPWT on untreated osteomyelitis is contraindicated. Application of NPWT to wounds containing necrotic tissue and eschar is contraindicated, and NPWT cannot be considered a substitute for thorough or repeated surgical debridement. Indeed, surgical debridement alone of superficial sternal wounds has been shown to result in significantly faster time to healing and reduced medical interventions compared with conventional wound care alone (L2), demonstrating the importance of this step of the clinical pathway.

Recommendation: NPWT ‘should’ be used only as an adjunctive therapy to combat wound infection (Grade B), Table 5.

NPWT should ‘not’ be used in isolation to treat wound infection but may be appropriate as an adjunct to other methods of infection control. Common methods of infection management include systemic antibiotic therapy, topical anti-microbials and serial debridement of infected or necrotic tissue. NPWT should be used on an infected wound only within an accepted clinical protocol for infection management, which includes one or more of these methods.

Where management of high levels of exudate is a specific treatment goal, a higher level of negative pressure, within the therapeutic range of 50–150 mmHg, may be needed to adequately manage the wound fluid. This is essential to ensure effective removal of fluid from the tubing into the waste canister. Determination of the correct level of pressure must be made on an individual basis. Examples of wounds which may be subject to high levels of exudate include but are not limited to explored high-output fistulas, fresh post-operative wounds, traumatic wounds and compartment syndrome. Experimental studies suggest that in a moderately exuding wound, pressure settings of –125 mmHg resulted in the maximal volume of fluid removal. Higher pressure (up to –175 mmHg) did not further increase the fluid removal (L3). The experimental model used was a non-infected, porcine excisional wound and could be expected to generate only moderate levels of fluid. In highly exuding wounds, such as those described above, circumstances can be envisaged where increases in negative pressure past –125 mmHg may be necessary to manage very large volumes of fluid. In a much earlier study, Usupov et al. (1987) monitored exudate removal at various negative pressures in rabbit wounds and concluded that optimal removal of wound exudate occurred at –75 to –80 mmHg. The reluctance to increase the level of negative pressure in this early study stemmed from the appearance of blood in the exudate, leading to the fear of haemorrhage.

Recommendation: To manage high levels of wound exudate or wound fluid, higher levels of negative pressure are recommended (Grade D) (Table 4 and Figure 1).
litterature, is paradoxical: several studies have applied NPWT to infected wounds as part of a wider treatment protocol usually employing serial debridement of necrotic tissue and/or antibiotic therapy, with good outcomes and resolution of many wound infections.36,44,91–93 However, other studies have monitored the ability of NPWT to reduce the wound bioburden, using microbiological techniques, and have found no reduction in bacterial numbers91,94,95 (L3), and four reported no change in bacterial numbers36,44,92,96 (L1) during the course of NPWT (Table 5).

Morykwas et al. (1997)62 demonstrated that application of NPWT to infected experimental porcine wounds reduced bacterial numbers significantly compared with a non-NPWT-treated control. This evidence has become the basis for the widespread belief that NPWT contributes towards bacterial clearance of infected wounds. However, none of the clinical studies published to date support this position. Of seven clinical articles that measure changes in bioburden following NPWT, three reported an increase in bacterial numbers91,94,95 (L3), and four reported no change in bacterial numbers36,44,92,96 (L1) during the course of NPWT (Table 5).

Weed et al. (2004),91 (L3), in a retrospective assessment of 25 patients, showed that bacterial levels during NPWT increased compared with levels measured pre- and post therapy. Moues et al. (2007)99 (L1) published a 54-patient RCT to assess bacterial load in wounds treated with NPWT or conventional saline gauze therapy. Although the size of the wounds decreased significantly faster in the NPWT group, no significant difference in total quantitative bacterial load was observed compared with the control group. Hu et al. (2009)44 compared patients treated with foam-based and gauze-based NPWT and reported that the bioburden of 75% and 70%, respectively, of patients did not change throughout the course of therapy, despite good wound outcomes.

However, despite reporting either no reduction or an increase in bacterial numbers, many of these studies identify the wounds to be responding favourably to NPWT.36,44,91,92 The action of NPWT on bacterial load may be secondary to other beneficial actions of NPWT including control of oedema, increased perfusion, wound contraction and granulation tissue formation. NPWT may have a different effect on different types of bacteria (Table 6). Several studies have suggested that the profile of wound bacteria changes as a result of NPWT.92,94,97 There is some consistency of evidence that NPWT may affect the bacterial balance of an infected wound in particular by decreasing the numbers of non-fermentative Gram-negative rods (which includes the common wound pathogen Pseudomonas aeruginosa) (Table 6).91,92 Only one animal study97 and one clinical study92 supports this observation, and further confirmation is needed. The clinical relevance of this observation also remains to be clarified. Observation of a single clinical case94 gave rise to some early concerns that NPWT may potentiate the growth of anaerobic species; this has since been refuted by a randomised trial,92 which reported no change in anaerobes following NPWT. The effect of NPWT on Staphylococcus aureus is less clear, with conflicting reports of increasing92 (L1) and stable bioburden94,97 (L3).

Another avenue to explore in the published literature relates to the relative incidence and resolution of clinically apparent infection in wounds treated with NPWT compared with those treated by alternative means. The most compelling evidence was presented by Stannard et al. (2009) (L1)98 who reported that open fracture wounds treated with NPWT between debridement procedures were one-fifth as likely as wounds treated with standard gauze dressing alone to develop a wound infection. This may have been either due to the ability of NPWT to prevent ingress of bacteria from external sources or due to the presence of the integral airtight drape or may indicate that application of NPWT to

| Table 5 Role of NPWT as an adjunct to infection management. |
|-----------------------------|-----------------------------|
| Treatment goal or variable  | Recommendation and Grade (A–D) | Reference (Evidence Level) |
| Unmanaged wound infection   | NPWT should be used only as  | B | L1*: 36, 44, 92, 96. |
|                            | an adjunctive therapy to   |   | L2: 95, 91. |
|                            | combat wound infection     |   | L3: 94. |
| Use of anti-microbial elements as part of the NPWT dressing/protocol | Anti-microbial gauze may contribute towards infection control | C | L1: 101b |
|                            | It is possible that Silver foam may contribute to infection control | D | L3: 105–109 |
|                            | When applied underneath the NPWT wound filler it is possible that anti-microbial WCL may contribute towards infection control | D | L2: 112, L3: 110, 111, 113. |
|                            | It is possible that fluid instillation may contribute to infection control | D | L3: 114–122. |

a Data extrapolated from Level 1 studies.

b Studies carried out on anti-microbial gauze in the absence of NPWT. Information from these studies can be extrapolated to support the benefits of anti-microbial gauze in addition to NPWT. Use of this data is valid because it describes the clinical efficacy of the exact dressing material provided as part of the majority of gauze-based NPWT commercial kits (Kerlix AMD gauze, Tyco).
contaminated wounds may prevent development of a latent clinical infection. A second RCT (L1)95 on pressure ulcers demonstrated a significantly faster resolution of osteomyelitis in NPWT-treated wounds compared with the comparator treatment. However, NPWT did not confer such an advantage in two RCTs carried out on diabetic foot ulcers: both Blume et al. (2008)99 and Armstrong et al. (2005)100 (L1+) reported no statistical significance in the incidence of clinical wound infection between wounds treated with NPWT and those treated with conventional saline gauze.

It does however appear certain that application of NPWT, within the appropriate clinical protocol, does not cause an increase in the rate of clinical infection. Furthermore, it might be hypothesised that improvement of the general condition of the wound will allow the patients' host defences to more effectively deal with colonisation or infection. Further investigation to fully establish this link is needed.

All studies to date, which report the effect of NPWT on wound microbiology, have been conducted using non-anti-microbial wound-filler materials. Any ability of these fillers to combat infection can at best only be either passive (e.g., hypothetical removal of non-adherent bacteria in the wound fluid) or secondary to the wider effects of NPWT (such as improved blood flow, granulation tissue formation and reduced oedema). However, other wound-filler variants are available, which confer more active anti-microbial properties on the wound. These include anti-microbial gauze and 'silver foam', which are discussed in more detail below:

**Recommendation:** anti-microbial gauze 'may' contribute towards infection control; **Grade C**; Table 5.

The most commonly used anti-microbial commercial variant is anti-microbial gauze, which is provided by several suppliers of NPWT (Table 5). The anti-microbial element is composed of 0.2% polyhexamethylene biguanide (PHMB). The dressing has proven clinically effective against a wide variety of wound pathogens in a series of studies in the absence of NPWT. Motta et al. (2004)101 reported the results of a randomised controlled multicentre trial investigating outcomes of using PHMB-impregnated gauze in the absence of NPWT compared with non-impregnated gauze. A greater reduction in both the total number of recovered microbial isolates and log colony counts was observed in the PHMB-gauze group. In an institute-wide audit study, the adoption of PHMB-impregnated gauze, instead of non-impregnated gauze, was observed to significantly reduce the incidence of post-surgical wound infection by 24%, including a 48% reduction in methicillin-resistant *Streptococcus aureus* (MRSA) infections (L2).102 These studies demonstrate that the addition of an anti-microbial element, here PHMB, to a conventional gauze dressing can impact significantly on the incidence and resolution of wound infection. No studies have compared the relative effect of PHMB-gauze and non-anti-microbial gauze when used in conjunction with NPWT. Several L3 studies have investigated the use of anti-microbial gauze-based NPWT and have tracked outcomes in terms of infection. No wound infections were reported in a non-comparative series of 30 patients.103 Other case series have reported significant reduction in the number of infected wounds compared with baseline, following treatment with anti-microbial gauze-based NPWT.103,104

**Recommendation:** it is 'possible' that silver foam may contribute to infection control; **Grade D**.

Silver foam (Granufloam Silver™, KCI) is a commercially available variant of PU foam for use in NPWT. It has been shown to be efficacious against *P. aeruginosa* and *S. aureus in vitro*105 (L3). It has been demonstrated in several L3 studies to result in good outcomes when applied to colonised or infected wounds.106–109 (L3). The defining feature of this clinical use of silver-foam-based NPWT is its application to wounds which either had positive cultures (colonised) or were clinically infected, as part of a wider clinical protocol. In all cases except one,109 wounds were debried prior to application of NPWT, and antibiotics were used in the majority of cases.106–109 In a case series of five patients treated (in part) with silver-foam-based NPWT in preparation for definitive closure of open fracture wounds, all patients had positive cultures at the onset of therapy. Following the application of silver-foam-based NPWT, negative cultures were returned in all patients between 5 and 9 days following the application of therapy.108

Several authors have also reported the application of silver-foam-based NPWT over STSG106,108,109 or dermal-replacement products106 in patients at high risk for infection. Application of an anti-microbial variant during this stage in high-risk patients seems like a sensible strategy, regardless of which anti-microbial wound-filler variant is used.

**Recommendation:** when applied underneath the NPWT wound filler, it is possible that anti-microbial WCL may contribute towards infection control; **Grade D**; Table 5.

A number of L3 studies have reported good clinical outcomes in the presence of an anti-microbial WCL in wounds at risk of infection110–113 (L3). The use of anti-microbial

### Table 6 Effect of NPWT on bacterial species.

<table>
<thead>
<tr>
<th>Bacterial species</th>
<th>Moues et al.92 (L1) RCT (n = 54)</th>
<th>Chester et al.94 (L3) Case (n = 1)</th>
<th>Khashram et al.95 (L3) Case series (n = 7)</th>
<th>Lallis et al.97 (L3) In vivo (n &gt; 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fermentative</td>
<td>Down</td>
<td>NR</td>
<td>NR</td>
<td>Down</td>
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<tr>
<td>rods (inc. P.</td>
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<td></td>
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<tr>
<td>aeruginosa)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacteraceae</td>
<td>←</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>(e.g. E.coli)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram positive</td>
<td></td>
<td>↑</td>
<td>←a</td>
<td>←a</td>
</tr>
<tr>
<td>S. aureus</td>
<td></td>
<td>←</td>
<td>None</td>
<td>NR</td>
</tr>
<tr>
<td>Non-specified</td>
<td>←</td>
<td>↑</td>
<td>↑</td>
<td>NA</td>
</tr>
<tr>
<td>Anaerobes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Bioburden</td>
<td>←</td>
<td>↑</td>
<td>↑</td>
<td>NA</td>
</tr>
</tbody>
</table>

*a* MRSA, NR = Not reported; None = non-identified. NA = Not applicable.

*b* Animal study where bacterial species were assessed in isolation. Overall bioburden was not measured.
wound fillers (either silver-foam- or anti-microbial gauze) to provide these benefits without the need for an additional WCL should also be considered. The relative benefits of applying an anti-microbial WCL beneath a standard wound-filler material compared with application of an anti-microbial wound filler alone have not been investigated.

**Recommendation:** It is possible that fluid instillation may contribute to infection control; **Grade D; Table 5.**

An emerging area in the literature describes the use of NPWT in combination with a fluid-instillation protocol. Fluid instillation consists of a closed wound dressing affixed to an NPWT pump with the facility to apply intermittent negative pressure. When pressure is stopped, the device can instil a fluid of choice (often an isotonic solution containing antibiotics or antibacterials) into the wound for the duration of the ‘off-cycle’. When negative pressure is resumed, the fluid is removed into the waste canister along with the wound fluid. Commercially available devices (L3) and also homemade devices (L3) have been reported to contribute towards infection management.

**Discussion**

In the past few years, there has been an expansion of the number of acceptable variables when applying NPWT. Key variables include a choice of wound-filler materials, the impact of selecting the correct pressure setting and when to use a WCL. The evidence base to identify the most appropriate usage of these variables, although growing, still largely consists of anecdotal observations and experimental studies. In light of this, consensus becomes an important part of recommendation generation. The recommendations here are restricted by the extent of the evidence base. However, it must be noted that many in vivo animal studies, classed as relatively low-grade studies (L3), are often statistically powered to detect differences between the variables being tested. Thus, many of the studies supporting these recommendations are more scientifically robust than suggested by the grade of recommendation allowed under the adopted system. Regardless, further well-designed comparative studies are required to further clarify the relative clinical benefits of the key questions in modern NPWT: which wound filler and pressure settings to select and when to use a WCL.

**Conflict of interest**

Authors Jenny Smith and Robin Martin are employees of Smith & Nephew. The International Expert Panel on Negative Pressure Wound Therapy (EP-NPWT) is funded by an unrestricted educational grant provided by Smith & Nephew. Where no further conflicts of interest are stated, none is known to exist. In addition to this funding, the following financial relationships exist: Norbert Runkel undertakes consultancy work for Smith & Nephew in educational and speaking engagements; Charles K. Lee undertakes consultancy work for Smith & Nephew in educational and speaking engagements; Hanne Birke-Sorensen has been member of two expert panels involving the use of NPWT but does not own shares or get any benefit from any company supplying NPWT; Raymond Dunn undertakes consultancy for and has received funding for clinical trials from Smith and Nephew; Steven Jeffery undertakes consultancy work for Smith & Nephew in educational and speaking engagements; Mark E. Chariker undertakes consultancy work for Smith & Nephew in the area of NPWT and has served as a fact witness in legal testimony; Caroline Dowsett undertakes consultancy work for Smith & Nephew; and Fernando Ferreira has received honoraria from Smith and Nephew and KCI Europe to train health-care professionals in the use of NPWT.

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