MIDDLE EAST CONSENSUS

WOUNDS INTERNATIONAL MIDDLE EAST EXPERT FORUM ON

NPWT IN INFECTED WOUNDS

Wound healing and infection

Evidence-based recommendations for NPWT in the prevention or management of infection

Using NPWT with instillation in practice

Proceedings from the Wounds International Middle East expert forum

WOUNDS MIDDLE EAST

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FOREWORD

Negative pressure wound therapy (NPWT) is an important option for the advanced management of many wound types[1]. Over recent years, NPWT has revolutionised care for many patients with chronic and acute wounds and this success has prompted the development of new types of NPWT system.

In November 2015, a group of clinicians from the Gulf region met in Dubai to discuss the role of NPWT in the management of infected wounds and to explore the potential for innovative NPWT systems to manage complex acute and chronic wounds.

Following the meeting, an initial draft of this document was developed and underwent review by the expert group. This final consensus represents the views of the expert group, and is designed to raise awareness of the role of NPWT in the management of complex wounds and provide recommendations for using NPWT in the prevention and treatment of infection in a range of wound types.

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Role of NPWT in the prevention and treatment of wound infection

WOUND HEALING AND INFECTION

Wound healing is a complex, multifaceted process that is influenced by intrinsic and extrinsic factors, some of which can be controlled.

The control and prevention of infection is critical for wound healing to occur

When a wound fails to progress to healing or respond to treatment over the expected healing time frame, and certain signs and symptoms are present, wound infection may be suspected[2].

Infection can have a substantial impact on patients' morbidity, mortality and length of stay in hospital. For example, according to a recent update to a collaborative expert guidance document entitled *Strategies to Prevent Surgical Site Infections in Acute Care Hospitals*[3], surgical site infections are now the most common and costly form of healthcare-associated infection (HAI)[4-6], accounting for up to 20% of all HAIs and occurring in at least 5% of patients undergoing a surgical procedure[7].

Wound infection occurs when host defence strategies are successfully invaded by microorganisms, which results in deleterious changes in the host[8]. Most wounds contain microorganisms and many heal normally; the potential for harmful effect of bacteria is influenced by the combative ability of the patient's immune system (host resistance), the number of bacteria present, and the virulence of the bacteria[2].

Recognising wound infection

The accurate identification of wound infection is a common clinical challenge. Both the patient and clinician require clarity and guidance to be able to recognise when the normal inflammatory process has become abnormal and whether this could be due to infection[9].

Microbiological assessment alone is not a reliable method for diagnosing wound infection; a full, holistic assessment of the patient is also required[8]. In 1994, Harding and Cutting developed a set of criteria to facilitate the identification of wound infection and emphasised the value of additional 'subtle' signs[10]. Shortcomings in the 1994 criteria became evident when it was observed that different wound types exhibited their own individual sets of criteria to indicate infection[8]. In addition, the classic signs of infection may not be obvious in patients who are immunocompromised, such as people with diabetes, or those with multiple health issues who develop chronic wounds[2].

In practice, wound assessment should incorporate a full evaluation of the patient that considers their immune status, comorbidities, wound aetiology, and any other factors that might affect risk, severity and potential signs of infection[2]. Figure 1 provides an overview of the signs and symptoms that may indicate wound infection in acute and chronic wounds.

Figure 1 | Signs and symptoms indicating wound infection in acute and chronic wounds[2]

ACUTE WOUNDS
eg surgical or traumatic wounds, or burns

Localised infection

- Classical signs and symptoms:
  - new or increasing pain
  - erythema
  - local warmth
  - swelling
  - purulent discharge
- Pyrexia – in surgical wounds, typically five to seven days post-surgery
- Delayed (or stalled) healing
- Abscess
- Malodour

Spreading infection

As for localised infection PLUS:
- Further extension of erythema
- Lymphangitis
- Crepitus in soft tissues
- Wound breakdown/dehiscence

Notes
- Burns – also skin graft rejection; pain is not always a feature of infection in full thickness burns
- Deep wounds – induration, extension of the wound, unexplained increased white cell count or signs of sepsis may be signs of deep wound (ie subfascial) infection
- Immunocompromised patients – signs and symptoms may be modified and less obvious

SYSTEMIC INFECTION

Sepsis – documented infection with pyrexia or hypothermia, tachycardia, tachypnoea, raised or depressed white blood cell count

↓

Severe sepsis – sepsis and multiple organ dysfunction

↓

Septic shock – sepsis and hypotension despite adequate volume resuscitation

↓

Death

NB: Other sites of infection should be excluded before assuming that systemic infection is related to wound infection

CHRONIC WOUNDS
eg diabetic foot ulcers, venous leg ulcers, arterial leg/foot ulcers or pressure ulcers

Localised infection

- New, increased or altered pain*
- Delayed (or stalled) healing*
- Periwound oedema
- Bleeding or friable (easily damaged) granulation tissue
- Distinctive malodour or change in odour
- Wound bed discoloration
- Increased or altered/purulent exudate
- Induration
- Pocketing
- Bridging

Spreading infection

As for localised infection PLUS:
- Wound breakdown*
- Erythema extending from wound edge
- Crepitus, warmth, induration or discoloration spreading into periwound area
- Lymphangitis
- Malaise or other non-specific deterioration in patient's general condition

Notes
- In patients who are immunocompromised and/or who have motor or sensory neuropathies, symptoms may be modified and less obvious. For example, in a diabetic patient with an infected foot ulcer and peripheral neuropathy, pain may not be a prominent feature
- Arterial ulcers – previously dry ulcers may become wet when infected
- Clinicians should also be aware that in the diabetic foot, inflammation is not necessarily indicative of infection. For example, inflammation may be associated with Charcot's arthropathy

*Individually highly indicative of infection. Infection is also highly likely in the presence of two or more of the other signs listed

A variety of tests are used to determine wound aetiology, comorbidities and wound condition, but current tests are not always able to determine the reason for non-healing in an optimally managed wound. At present, new diagnostic tests are in development that will offer alternative approaches to diagnosing wound infection, including:

- Temperature mapping in chronic wounds – high temperature gradients between feet may predict the onset of neuropathic ulceration; a study by Armstrong et al (2008)[11] suggested that skin temperature self-monitoring may reduce ulceration risk in patients with diabetes
- Measuring cytokine levels in chronic wounds that are clinically infected[12].

Identifying infection severity

Once a diagnosis of wound infection has been confirmed, level of severity should be determined.

The presence of bacteria in a wound may result in[2]:

- Contamination – bacteria are present but do not increase in number of cause clinical problems
- Colonisation – bacteria multiply and healing is disrupted but there is no tissue damage
- Infection – bacteria multiply, healing is disrupted and wound tissues are damaged.

It is important to differentiate between different stages in this wound healing continuum (Figure 2) to determine requirement for increased vigilance and local or systemic therapies, since an untreated superficial infection can potentially become a deep infection and systemic, and result in sepsis[2].

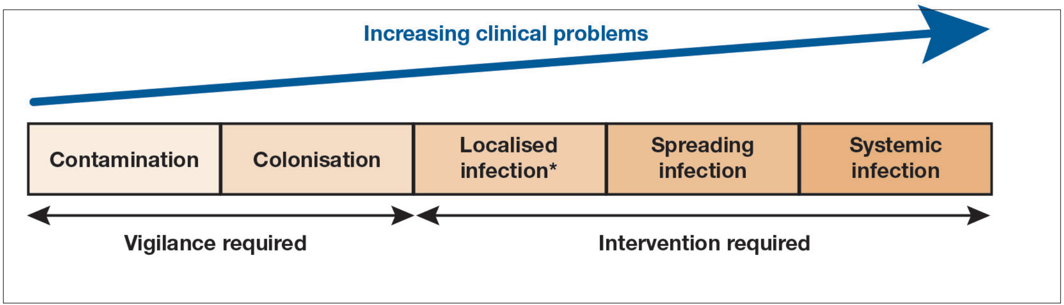


Figure 2 | Interaction between bacteria and host, with increasing requirement for vigilance and intervention (adapted with permission[13])

NB: localised infection has also been described as 'critical colonisation' or 'local infection'. Localised infection may or may not be accompanied by the classical signs or symptoms of infection; where it is not, some clinicians may use the term 'critical colonisation' to refer to this more subtle state.

The focus should be on establishing whether the infection will be potentially severe or devastating and will require treatment with antibiotics, or whether the wound can be managed with less intervention and avoidance of unnecessary antibiotic treatment. In 2015, the World Health Organisation published a *Global Action Plan on Antimicrobial Resistance*, reflecting the importance of ensuring the continuity of successful antimicrobial treatment, and highlighting the urgency of tackling antimicrobial resistance by developing antibiotic stewardship. Resistance develops more rapidly through misuse and overuse of antimicrobial medicines[14]. Therefore, it is important to stratify patients according to increased risk and severity of infection[15].

The *Clinical Practice Guidelines for Diagnosis and Treatment of Diabetic Foot Infections* (2012)[15] presents one such severity classification system that helps determine the level of care a patient with a diabetic foot infection should receive. Levels of severity are as follows:

- Mild infection – superficial and limited in size and depth
- Moderate infection – deeper or more extensive (compared with mild)
- Severe infection – accompanied by systemic signs or metabolic.

According to this system, patients whose infection status is more severe will require a more aggressive approach to treatment (i.e. hospitalisation, specialist imaging procedures, surgical interventions, or amputation)[15].

However, selecting the right treatment is challenging. In treatment of the diabetic foot ulcers, for example, there is a lack of data to support use of a particular antibiotic agent, treatment strategy, route of administration or duration of therapy[16]. Moreover, it is worth noting that similar classification guidelines do not exist for other wound types.

ADVANCES IN NPWT

Negative pressure wound therapy (NPWT) works by applying localised negative pressure to the wound bed through a polyurethane reticulated open-cell foam dressing or a polyvinyl alcohol foam dressing, allowing equal distribution of negative pressure across the entire wound bed. When used in conjunction with appropriate wound bed preparation, the basic modes of action include:

- Promoting granulation tissue formation
- Stimulating cell perfusion
- Promoting tissue oxygenation
- Removing wound exudate and infectious materials
- Reducing localised oedema
- Providing a closed moist wound environment with a sealed system
- Promoting wound contraction[17].

Since its introduction, NPWT has led to improved wound care outcomes and, over the past decade, has dramatically changed the way complex wounds are treated[2]

NPWT has evolved considerably and has been used to treat a variety of wound types. There is an established evidence base for NPWT, with many peer-reviewed papers published on its efficacy and safety[18]. A MEDLINE search undertaken on 31 October 2015 identified approximately 3000 papers from over 60 countries reporting on its use in 100 indications.

Since NPWT is accessible to 75% of the global population (according to the aforementioned MEDLINE search), there is a need to clarify which patients should be receiving it, in order to ensure appropriate usage. Current indications for NPWT include chronic, acute and subacute wounds, including pressure and diabetic ulcers, partial thickness burns, dehisced wounds, flaps and grafts[19].

NPWT can be considered when the wound is not progressing in the expected time frame, is producing high levels of exudate that are difficult to manage, is in a difficult location or is a large size making it difficult to achieve an effective seal with a traditional dressing, or requires reduction in size to achieve surgical closure[20;21]. In addition, in certain wound types and with skin grafts, NPWT can provide rigid support, conferring a splinting effect[22].

Randomised clinical trials (RCTs) support the use of NPWT in certain wound types[23-25], although the overall evidence is weak[26]. However, the clinical evidence base is growing as NPWT becomes more widely utilised worldwide.

Use of NPWT in infected wounds

Use of NPWT for the management of infected wounds should not be considered as a standalone option. However, NPWT may be used with caution in infected wounds, as long as this is additional to appropriate treatment of the infection. Indeed, a number of publications report its benefits in the management of colonised or infected wounds when used as an adjunct to other infection control methods[27]. These findings have led to growing interest in the use of innovative modalities of NPWT for the prevention and management of infection.

There are a number of additional factors to consider when NPWT is used in the presence of infection, including:

- Debridement or removal of devitalised tissue
- Appropriate antibiotic therapy
- Frequent assessment of the patient and wound
- Increased frequency of dressing changes
- Appropriate pressure settings on the NPWT system
- Periwound skin protection
- Use of fenestrated antimicrobial dressings[1].

It is important to consider whether systemic antibiotic therapy is required or if it may be appropriate to first treat the wound infection according to local protocol[1]. If used in deep wound infection, NPWT should always be used in combination with systemic antibiotics and should be implemented as early as possible after surgical debridement[27]. NPWT is contraindicated in untreated osteomyelitis[28]. In some cases, clinicians may not be able to prescribe antibiotics after a surgical debridement; for example, in the case of multi-resistance (4MRGN). In this instance, debridement and antiseptics should be combined without antibiotics.

Where infection is persistent or wounds exhibit no progress towards healing, it is recommended that the wound is reassessed (including microbiological assessment) and treatment discontinued. If infection develops during therapy, treatment should be discontinued and systemic antibiotics considered[29].

SECTION SUMMARY

- The presence of wound infection has a substantial impact on morbidity, mortality, and length of stay in hospital, with surgical site infections now the most common and costly form of HAI.
- Microbiological assessment alone is not a reliable method for identifying wound infection; assessment should also include full wound evaluation and a holistic patient evaluation, considering immune status, comorbidities, wound aetiology, and factors that might affect risk and severity of infection.
- New diagnostic tests are in development that will offer alternative approaches to diagnosing wound infection, including temperature mapping in chronic wounds and measurement of cytokine levels in chronic wounds that appear to be clinically infected.
- Increased emphasis on severity of infection is required, with a focus on establishing whether the infection may become severe or devastating and require antibiotics, or whether antibiotic treatment can be avoided.
- NPWT is an important development in advanced wound care, and is increasingly utilised globally. Although NPWT should not be used as a standalone option for infected wounds, numerous publications have reported its benefits when used as an adjunct to other infection control methods.

Evidence-based recommendations for NPWT in the prevention or management of infection

This section will cover variations of NPWT available for the following uses

1. Closed incisional wounds that are at a high risk of infection
2. Contaminated open wounds that are at high risk of infection or critical colonisation/local infected/localised infection
3. Open wounds that are colonised or infected, with instillation.

Table 1 outlines factors that may be associated with surgical site infection risk and should be considered when assessing a patient's suitability for ciNPT.

NPWT FOR CLOSED SURGICAL INCISIONS AT HIGH RISK OF INFECTION

A number of patient-specific or operation-related factors can make the management of surgical wounds challenging, due to increased risk of complications such as infection[30]. Patients who are at risk of such complications may benefit from use of a closed incisional negative pressure therapy system (ciNPT) post-operatively, to prevent infection in wounds that continue to drain. Potential for complications such as infection can inform the decision as to when ciNPT may be used to protect a closed surgical incision. However, there is no defined threshold for when to use ciNPT (i.e. which patients are at the greatest risk) and therefore clinical judgement is vitally important. Clinical judgement is based on individual experience of selecting patients at high risk of infection or those for whom the consequences of infection might be greatest. There is a need to prevent over-use and provide clear guidelines on appropriate usage.

Table 1: Factors that may be associated with surgical site infection[31]

Patient-related factor	Operation-related factor
Older age	Inadequate preparation of the skin, such as inappropriate preoperative shaving
Malnutrition	Inadequate antisepsis
Diabetes	Contaminated surgical environment; inadequate sterilisation of instruments
Active smoker	Inappropriate surgical attire
Obesity	Excessive length of operation
Colonisation with microorganisms	Poor technique: excessive blood loss, hypothermia, tissue trauma, devitalised tissues, entry into hollow viscus, dead space
Co-existing infection at a remote location	Presence of surgical drains and suture material
Altered immune response	Inappropriate or untimely antimicrobial prophylaxis
Pre-operative hospitalisation	High risk incisions (such as sternotomy wounds)

Clinical evidence

Effective use of ciNPT has been demonstrated across a variety of wound types, using systems such as the Prevena™ Incision Management System (Acelity).

Table 2 summarises current evidence from RCTs for management with ciNPT

In some studies, uncertainty remained around the benefit of ciNPT, but the majority demonstrated positive effects, including:

- Decreased drainage
- Improved wound healing
- Increased perfusion
- Decreased development of postoperative seromas
- Decreased incidence of wound dehiscence
- Decreased incidence of acute and total infections
- Reduced total wound secretion days
- Reduced time and materials required for wound care.

Table 2: Summary of RCT evidence for ciNPT

Ref	Title	Aim	Method	Main findings
Stannard et al, 2006[32]	Negative pressure wound therapy to treat hematomas and surgical incisions following high-energy trauma	To evaluate the use of ciNPT to augment healing of surgical incisions and haematomas after high-energy trauma	Patients with draining haematomas (n=44) treated with pressure dressing or ciNPT therapy (VAC). Patients with calcaneus, pilon, and high-energy tibial plateau fractures (n=44) treated with standard postoperative dressing or VAC	Decreased drainage and improved wound healing following haematomas and severe fractures with ciNPT. Potential mechanisms of action include angiogenesis, increased blood flow, and decreased interstitial fluid
Atkins, 2011[33]	Laser Doppler flowmetry assessment of peristernal perfusion after cardiac surgery: beneficial effect of negative pressure therapy	To evaluate peristernal perfusion after cardiac surgery via median sternotomy (using laser Doppler flowmetry), assessing the influence of ciNPT (and mammary artery harvesting)	ciNPT (n=10) compared with standard dressings applied to control incisions (n=10) in patients with increased risk for wound complications	ciNPT increased perfusion relative to controls and compensated for reduced perfusion rendered by mammary artery harvesting, providing additional support for 'well wound therapy' in high-risk patients
Howell et al, 2011[34]	Blister formation with negative pressure dressings after total knee arthroplasty (TKA)	To assess benefits of ciNPT in the immediate postoperative period after TKA in high-risk patients	ciNPT (n=24) compared with sterile gauze dressing (n=36) in 51 patients undergoing 60 TKA surgeries (nine bilateral)	ciNPT did not appear to hasten wound closure and was associated with blisters. There did not appear to be a benefit to the routine use of NPWT in the immediate postoperative period
Masden, 2012[35]	Negative pressure wound therapy for at-risk surgical closures in patients with multiple comorbidities: a prospective randomized controlled study	To evaluate the effect of ciNPT on closed surgical incisions	ciNPT (n=44) compared with standard dry dressings (n=37) on surgical incisions	No difference in the incidence of infection or dehiscence between the ciNPT and dry dressing groups
Pachowsky, 2012[36]	Negative pressure wound therapy to prevent seromas and treat surgical incisions after total hip arthroplasty (THA)	To evaluate use of ciNPT to improve wound healing after THA and influence on development of postoperative seromas in the wound area	Prospective randomised evaluation compared a standard dressing (n=10) with ciNPT (n=9) in patients with large surgical wounds	Decreased development of postoperative seromas in the wound and improved wound healing with ciNPT
Stannard et al, 2012[37]	Incisional negative pressure wound therapy after high-risk lower extremity fractures	To investigate ciNPT to prevent wound dehiscence and infection after high-risk lower extremity trauma	Prospective multicentre trial compared ciNPT (n=141) with standard postoperative dressing (n=122) in patients with high-risk fractures (tibial plateau, pilon, calcaneus)	Decreased incidence of wound dehiscence and total infections after high-risk fractures for patients who had ciNPT applied to their surgical incisions after closure, and a strong trend for decrease in acute infections after ciNPT
Grauhan et al, 2013[38]	Prevention of poststernotomy wound infections in obese patients by negative pressure wound therapy	To evaluate ciNPT treatment for the prevention of infection	Prospective study compared ciNPT with conventional wound dressings in obese patients (body mass index >/= 30) with cardiac surgery performed via median sternotomy	ciNPT treatment over clean, closed incisions for the first 6 to 7 postopera-tive days reduced incidence of wound infection after median sternotomy in a high-risk group of obese patients
Pauser et al, 2014[39]	Incisional negative pressure wound therapy after hemiarthroplasty for femoral neck fractures - reduction of wound complications	To evaluate ciNPT in wound healing after femoral neck fracture treated with hip hemiarthroplasty, including influence on seromas, wound secretion, and time and material consumption	Prospective randomised study compared ciNPT (n=11) with a standard wound dressing (n=10)	Decreased development of postoperative seromas, reduction of total wound secretion days and reduction of time required for dressing changes with ciNPT
Gillespie et al, 2015[40]	Use of negative-pressure wound dressings to prevent surgical site complications after primary hip arthroplasty: a pilot RCT	To assess use of ciNPT on surgical sites to prevent infections and other wound complications after elective primary hip arthroplasty and to consider feasibility of a larger trial	Non-masked, prospective trial compared ciNPT (n=35) with a standard hydrocolloid reinforced with two absorbent dressings (n=35)	A reduction of 3% in surgical site infection incidence suggests a definitive trial requires approximately 900 patients per group. However, there is uncertainty around the benefit of ciNPT after elective hip arthroplasty — dressing costs were lower in the control group and ciNPT patients experienced more postoperative wound complications
Nordmeyer et al, 2015[41]	Negative pressure wound therapy for seroma prevention and surgical incision treatment in spinal fracture care	To evaluate the clinical use and economic aspects of ciNPT after dorsal stabilisation of spinal fractures	Prospective randomised evaluation compared ciNPT (n=10) with standard dressing (n=10) in patients with large wounds after surgical stabilisation of spinal fractures by internal fixation	ciNPT reduced the development of postoperative seromas, reduced nursing time and reduced materials required for wound care

The Prevena Incision Management System creates an environment that promotes healing, draws the closed incision edges together, stimulates perfusion, reduces lateral tension and oedema, and acts as a barrier to external contamination[42].

A number of studies have provided evidence for Prevena; main findings are reported below

Case reports:

- Prevena was conveniently and safely implemented on operational incisions in renal transplant recipients (n=52) to prevent surgical wound complications[43]
- A low wound complication rate was seen in closed Pfannenstiel incisions at time of caesarean section (n=26), with no cases of sheath dehiscence and no patients requiring a second operation[44]
- Prophylactic ciNPT was delivered successfully over high-risk, clean surgical incisions (n=62)[45]
- In a prospective case-control study of patients undergoing vascular bypass procedures (n=8), no significant wound complications occurred in wounds treated with surgical incision management, compared with three significant complications in control wounds[46]
- Surgical incision management over clean, closed incisions for the first 6-7 postoperative days substantially reduced the incidence of wound infection after median sternotomy (prospective study [n=237]; retrospective study [n=3508])[47]
- Treating wounds with Prevena post-operatively led to a remarkable reduction of wound complications following open pectus surgery (n=100)[48]
- A patient with persistent postoperative serous wound secretion after femoral nailing was treated successfully[49]
- No patients had postoperative surgical wound dehiscence following pathological scar excision after treatment (n=8)[50]
- The incidence of groin wound infection substantially decreased in patients after vascular surgery (n=115)[51]
- In patients with surgical incisions after cardiac surgery, complete healing was achieved with the absence of skin lesions, and no wound complications occurred until at least 30 days after surgery (n=10)[52]

Porcine models:

- Early application of Prevena improved the quality of healed porcine incisions in terms of mechanical, histomorphometric, and gene-expression properties[53]
- Application on closed porcine incisions presented a trend toward improved early healing strength, and in significantly improved incision appearance[54]

Literature reviews:

- A systematic review of the literature showed a decrease in the incidence of infection, sero-haematoma formation and on reoperation rates when using ciNPT (as delivered by Prevena and a competitor product). A lower level of evidence was found on dehiscence and was inconsistent, so a conclusion could not be made in this instance[30]. Another literature search revealed that there are increasing numbers of studies describing Prevena's use in applications including vascular, cardiac and orthopaedic[55].

NPWT FOR CONTAMINATED OPEN WOUNDS THAT ARE AT HIGH RISK OF INFECTION OR CRITICAL COLONISATION/LOCAL INFECTION/LOCALISED INFECTION

There is some clinical evidence to support the use of standard NPWT in conjunction with open-cell foam dressing in the management of critical colonisation/local infection/localised infection.

In a prospective randomised study of 59 patients with 63 severe, high-energy open fractures, patients treated with standard NPWT therapy were compared with a control group (treated with irrigation plus debridement repeated every 48–72 hours, and a standard fine mesh gauze dressing, until wound closure) to measure the presence or absence of deep wound infection or osteomyelitis, amongst other outcomes (wound dehiscence and fracture union)[56]. Control patients developed two acute infections and five delayed infections (seven deep infections [28%]), while NPWT-treated patients developed no acute infections and only two delayed infections (two deep infections [5.4%]. These results suggest that NPWT is promising therapy option for severe open fractures, with a significant difference between the groups for total infections (p=0.024) and a relative risk ratio of 0.199 (95% CI: 0.045-0.874)[56].

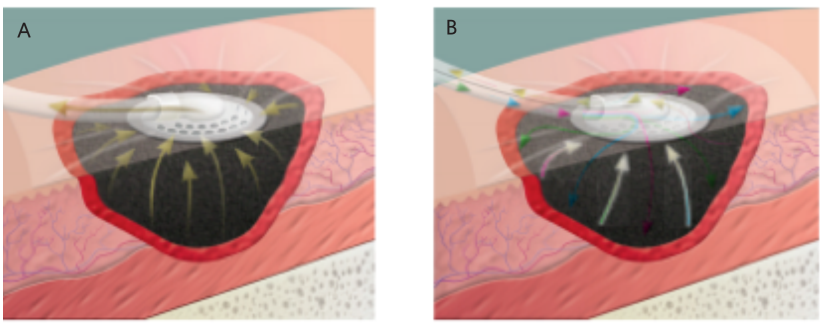
When used in the management of critically colonised wounds, it is recommended that prior to application of NWPT all devitalised tissue is debrided, the wound has adequate perfusion, and the patient is free from signs of systemic infection[27]. Use of a silver-impregnated foam may offer an additional antimicrobial effect[27], although judicious use of silver dressings is recommended[57].

Although use of NPWT with instillation in non-infected wounds is not widespread at present, it is possible to give first temporary recommendations on antiseptic-based NPWT with instillation, based on the available scientific literature. If there is a need for antisepsis (e.g. in contaminated wounds, such as gun shot wounds or animal bites) and the patient is being cared for in a hospital setting, stepping up to treatment to NPWT with instillation using an antiseptic solution is recommended[58].

USING NPWT WITH INSTILLATION THERAPY FOR INFECTED OPEN WOUNDS

Negative pressure with instillation (V.A.C.Ulta™, Acelity) (Figure 3) combines established NPWT with an advanced system allowing for automated, controlled delivery and removal of topical wound instillation solutions at the wound bed. These solutions are left to rest for a short period of time and then removed during a cycle of NPWT. The modes of action of standard NPWT and NPWT with instillation are depicted in Figure 3.

Figure 3 | Modes of action of standard NPWT (A) and NPWT with instillation (B)[59]



A: Standard NPWT — uses a vacuum to deliver negative pressure to the wound bed

B: NPWTi — topical solutions are delivered to the wound bed for a defined period before being removed by negative pressure

NPWT with instillation can be used with saline or antimicrobial agents that have been assessed for device compatibility to reduce the potential for wound infection[59]. The decision as to whether to use standard NPWT or NWPT with the addition of instillation therapy should be based on the need for wound cleansing or treatment with topical antiseptics.

The cyclic nature of NPWT with instillation allows the clinician to set the exact amount of solution to be delivered to the wound bed during instillation. During the 'off-cycle', the solution is held in the foam dressing (wound filler) for a set period, before negative pressure is resumed, removing the fluid along with exudate and potentially harmful substances into the canister. This process can be repeated as often as required to ensure optimal contact of the instillation fluid with the wound bed[58].

Benefits of using NPWT with instillation include:
- Decontamination of the wound
- Assistance with wound bed preparation
- Increased granulation tissue
- Temporary wound closure, and allows second look (as with standard NPWT).

Practical recommendations for use of NPWT with instillation are provided in Section 3 of this document

Clinical evidence

Recent studies have reported positive results for NPWT with instillation when combined with debridement and systemic antibiotics in a range of wound types, including:

- Extremity and trunk wounds[60]
- Acutely infected wound[61]
- Chronic lower leg and foot wounds[62]
- Numerous types of complex wound, including open fractures, pressure ulcers, and non-healing postoperative wounds[63;64]
- Open, contaminated or infected wounds[65]

Table 3 provides a summary of comparative evidence for NPWT with instillation versus standard wound therapy or standard NPWT, demonstrating the following positive outcomes

- Reduction in bioburden
- Decreased time to wound closure
- Reduced infection rates
- Decreased length hospital stay
- Fewer additional surgical procedures
- Improved cleansing and exudate removal.

BOX 1 | Difference between instillation and manual irrigation

Irrigation: Washing of a body cavity or wound by a stream of water or other fluid. A steady, gentle stream is used, e.g. manual irrigation of the wound with the gentle use of a syringe.

Instillation: Procedure by which a fluid is slowly introduced into a cavity or passage of the body and allowed to remain for a specific length of time before being drained or withdrawn. It is performed to expose the tissues of the area to the solution or a drug substance in the solution, e.g. via NPWT.

TABLE 3 | Comparative evidence for NPWT with instillation versus standard wound therapy or standard NPWT

Reference	Title	Aim	Method	Main findings
NPWT with instillation versus standard wound therapy				
Gabriel et al, 2008[66]	Negative pressure wound therapy with instillation: a pilot study describing a new method for treating infected wounds	To review 15 patients treated with VAC NPWT in addition to the timed, intermittent delivery of an instilled topical solution for management of complex, infected wounds	NPWT with instillation (n=15) compared with a standard moist wound care therapy (n=15)	NPWT with instillation led to a significant decrease in mean time to bioburden reduction, wound closure and hospital discharge compared with traditional wet-to-moist wound care
Timmers et al, 2009[67]	Negative pressure wound treatment with polyvinyl alcohol foam and polyhexanide antiseptic solution instillation in posttraumatic osteomyelitis	To assess the clinical outcomes of patients with osteomyelitis treated with NPWT with instillation	Retrospective, case-control cohort study compared NPWT with instillation (n=30) with a control group (n=94)	In the instillation group, rate of infection recurrence was lower, length of time in hospital was shorter, and number of surgical procedures smaller compared with controls. NPWT with instillation reduces the need for repeated surgical interventions in postoperative osteomyelitis compared with the standard approach
NPWT with instillation versus standard NPWT				
Gabriel et al, 2014[60]	Use of negative pressure wound therapy with automated, volumetric instillation for the treatment of extremity and trunk wounds: clinical outcomes and potential cost-effectiveness	To compare clinical outcomes of wounds treated with NPWTi-d (instillation and dwell time) versus NPWT and to estimate cost differences between treatments based on clinical outcomes	Retrospective analysis of patients with extremity or trunk wounds treated with NPWT (n=34) or NPWTi-d using saline or polyhexanide (n=48)	NPWTi-d appeared to assist in wound cleansing and exudate removal, which may have allowed for earlier wound closure compared with NPWT
Goss et al, 2012[62]	Negative Pressure Wound Therapy With Instillation (NPWTi) Better Reduces Post-debridement Bioburden in Chronically Infected Lower Extremity Wounds Than NPWT Alone	To assess the efficacy of wound bed preparation on wound bioburden with NPWT or NPWT with instillation	Prospective pilot study of patients with lower leg or foot wounds (n=16) compared sharp surgical debridement followed by NPWT or NPWT with instillation	Wounds treated with NPWT with instillation (quarter strength bleach solution) had a statistically significant reduction in bioburden, while wounds treated with NPWT had an increase in bioburden over the 7 days
Kim et al, 2014[61]	The impact of negative-pressure wound therapy with instillation compared with standard negative-pressure wound therapy: a retrospective, historical, cohort, controlled study	To evaluate the impact of NPWT with or without instillation on acutely and chronically infected wounds	Retrospective, historical, cohort-control led study examined the impact of NPWT with instillation (n=34) compared with standard NPWT (n=74)	NPWT with instillation (6- or 20-minute dwell time) is more beneficial than standard NPWT for the adjunctive treatment of acutely and chronically infected wounds that require hospital admission
Tao et al, 2014[68]	VAWCM-Instillation Improves Delayed Primary Fascial Closure of Open Septic Abdomen	To evaluate the effect of combined therapy of vacuum-assisted mesh-mediated fascial traction and topical instillation on delayed primary fascial closure (DPFC) in the open septic abdomen (OA)	Retrospective cohort study compared patients with abdominal sepsis who underwent OA using VAWCM (n=73) and instillation with a non-instillation control group (n=61)	Mortality with OA was similar between the two groups, but time to DPFC (p=0.003) and length of stay in hospital (p=0.022) of survivals were significantly decreased in the instillation group. Moreover, VAWCM-instillation (OR 1.453, 95% CI 1.222-4.927, P = 0.011) was an independent influencing factor related to successful DPFC
Wen et al, 2015[69]	[Effects of vacuum sealing drainage combined with irrigation of oxygen loaded fluid on wounds of pa- tients with chronic venous leg ulcers]	To evaluate the effects of vacuum sealing drainage (VSD) combined with irrigation of oxygen-loaded fluid on the growth of granulation tissue and macrophage polarisation in chronic venous leg ulcers	Study compared patients with chronic venous leg ulcers treated with VSD (n=11), VSD + irrigation (n=11), or VSD + oxygen-loaded fluid irrigation group (n=12)	VSD combined with irrigation of oxygen-loaded fluid raises the partial pressure of oxygen of the skin around wounds effectively, promoting transition of macrophages from type I to type II; thus, it may promote growth of granulation tissue, resulting in a better recipient for skin grafting or epithelisation

TABLE 4 | *In vitro* and animal model evidence for V.A.C Ulta and V.A.C VeraFlo

Reference	Title	Aim	Method	Main findings
Lessing et al, 2011[70]	Negative pressure wound therapy with controlled saline instillation (NPWTi): dressing properties and granulation response *in vivo*	Effect on granulation tissue formation	*In vivo* pig model with full thickness wounds (5cm diameter) evaluated granulation tissue thickness over a 7-day period	After 7 days, a significant increase in granulation tissue thickness was seen (43%; $p<0.05$)
Rycerz et al, 2013[71]	Distribution assessment comparing continuous and periodic instillation in conjunction with negative pressure wound therapy using an agar-based model	Distribution of instillation fluid over the wound bed	Benchtop agar wound models with and without tunnelling and undermining	Periodic V.A.C. VeraFlo therapy allowed better solution distribution across the wound surface, including tunnels and undermining, when compared with irrigation
LaBarbera et al, 2012[72]	The effects of pulsed lavage and instillation therapies on porcine wounds	Effects of wound cleansing on tissue damage	*In vivo* pig model with full-thickness wounds (5cm diameter) allowed to granulate for 5 days	V.A.C. VeraFlo therapy resulted in less tissue swelling (i.e. decrease in wound volume)

Table 4 summarises evidence for V.A.C Ulta and V.A.C VeraFlo™ derived from *in vitro* and animal models

SECTION SUMMARY

- Patients with closed incisions who are at risk of surgical complications such as infection may benefit from ciNPT in the post-operative period. Evidence from numerous RCTs has demonstrated successful outcomes of ciNPT in various wound types.
- There is evidence that standard NPWT may be useful in the management of open wounds that are at high risk of infection or critical colonisation/local infection/localised infection. Where a wound is not infected but there is a need for antisepsis, such as in contaminated wounds, stepping up to NPWT with instillation in a hospital setting may be recommended.
- NPWT with instillation can be used for open wounds that are colonised or infected, with the decision to use instillation therapy based on the need for wound cleansing or treatment with topical antiseptics. When compared with standard wound therapy or standard NPWT, NPWT with instillation has shown a number of benefits, including reduced bioburden and wound infection rates.

TABLE 5: Additional clinical evidence for NPWT plus instillation

Reference	Title	Aim	Method	Main findings
Bernstein, 2005[73]	Combination of sub-atmospheric pressure dressing and gravity feed antibiotic instillation in the treatment of post-surgical diabetic foot wounds	Effect of NPWT with instillation (saline, polymyxin B and bacitracin) in diabetic foot wound	Six hours of NPWT followed by instillation therapy was applied to five wounds	Decrease in hospital stay and amputation rate was seen with NPWT with instillation
Schintler et al, 2009[74]	The impact of V.A.C. Instill® in severe soft tissue infections and necrotizing fasciitis	Effect of NPWT with instillation (polyhexanide) in patients with skin and soft tissue infections	Series of 15 patients were treated with NPWT and instillation therapy	Infection was controlled and complete healing achieved in all patients
Lehner et al, 2011[75]	First experiences with negative pressure wound therapy and instillation in the treatment of infected orthopaedic implants: a clinical observational study	Effect of NPWT with instillation (polyhexanide) on orthopaedic implant retention following acute or chronic infection	Observational study of 32 patients with an infected orthopaedic implant treated with NPWT with instillation (polyhexanide)	Following treatment, 19 patients (86%) with acute infection and eight patients (80%) with a chronic infection retained their implant at 4- to 6-month follow-up
Dondossala et al, 2015[76]	Negative Pressure wound treatment of infections caused by extensively drug-resistant gram-negative bacteria after liver transplantation: two case reports	Effect of NPWT with instillation on patients with wound infection following liver transplant	Case study of two patients with infection caused by extensively drug-resistant Klebsiella pneumonia treated with NPWT with instillation	After NPWT with instillation, a reduction in bacterial load and exudate was observed with reduction in inflammatory markers. Complete healing was achieved and both patients are currently alive
Wolvos, 2013[65]	The use of negative pressure wound therapy with an automated, volumetric fluid administration: an advancement in wound care	Review of clinical experience with a system combining NPWT and NPWT with instillation	Pilot study of six patients treated with NPWT with instillation (and one of two dressings; instillate: Microcyn® antiseptic solution or quarter- strength Dakin's Solution®), and one patient treated with NPWT (and a third dressing)	The system worked well across multiple wound types in either NPWT or NPWT with instillation mode, and no complications were observed
Rycerz et al, 2013[77]	Science supporting negative pressure wound therapy with instillation	To review updates in the science supporting NPWT with instillation	Summary of the 2012 and 2013 International Surgical Wound Forum presentations based on recently published scientific literature, including results of benchtop and preclinical studies in NPWT with instillation	Benchtop data suggest that NPWT with instillation allowed for effective distribution and uniform exposure of topical wound solutions; *in vitro* data for NPWT with instillation indicated bacterial aerisolisation might be minimised; porcine models suggested that NPWT with instillation cleansed wounds as effectively as low-pressure lavage while reducing oedema; and increased granulation tissue formation compared with NPWT was observed
Wachal et al, 2013[78]	The Application of Negative Pressure Wound Therapy with Installation in Diabetic Foot Associated with Phlegmon	To evaluate the benefits of NPWT and drainage flow in a patient with diabetic foot complications	Case study of a patient treated with NPWT with instillation (V.A.C. Ulta) for ischaemic diabetic foot syndrome complicated by phlegmon and tissue necrosis	Patient was discharged with a completely healed wound and has regained full mobility

Table 5 presents a summary of additional clinical evidence for NPWT plus instillation.

Using NPWT with instillation in practice

CONSIDERATIONS FOR USE OF NPWT WITH INSTILLATION

Optimal interface material

A polyurethane wound filler is recommended where rapid granulation tissue formation is desired[26]. The ideal wound filler has an open-pore structure, remains intact during instillation therapy, and enhances fluid delivery and removal. It is important to protect the surrounding skin around the wound (i.e. using hydrocolloids)[58].

Time and duration of irrigation

At present, there are no guidelines for the optimal time to begin NPWT with instillation, although early intervention is important. A recent study showed that debridement of extremity wounds should take place as soon as possible, followed by lavage-irrigation using low pressure delivery systems[79].

Duration of NPWT with instillation treatment depends on factors such as wound quality and the surgical plan, although indefinite use may not be clinically or economically advisable[80]. There is published evidence for duration of use between 1 and 3 weeks[81].

Choice of pressure level

In the traditional continuous mode for V.A.C Ulta, negative pressure is usually applied at a setting in the range of -25mmHg to -200mmHg[59]. The appropriate negative pressure setting will be affected by nutritive perfusions of the tissue; where these are normal, -125 mmHg is suggested, but higher levels of hypoxia will require the pressure to be lower (as low as -50 mmHg).

The V.A.C Ulta system also has a Dynamic Pressure Control™ mode, which allows for cycles of negative pressure to be applied to the wound bed — this mode maintains a low level of negative pressure (-25 mmHg) at the wound bed between cycles to avoid any risk of leaks and fluid accumulation[59].

Amount of instillation solution required

The ideal volume of instillation fluid matches the size of the wound, but this is variable since wounds differ in size and are irregular in their dimensions: too much solution may make it difficult to maintain an appropriate seal with the dressing and could lead to maceration of the surrounding tissue, but too little may mean that the entire wound surface is not bathed in solution. It is suggested that a range between 20 and 100mL is suitable, or until the foam is visibly saturated[80].

Length of negative pressure cycles and dwell time

It is suggested that an appropriate instillation dwell time is within the range of 10 to 20 minutes. At present, there is no evidence that evaluates the relationship between dwell time and antimicrobial dressing activity when a solution is used in combination with NPWT[80].

A balance should be reached between the length of dwell time of the instillation fluid and the length of time over which negative pressure is applied. An appropriate negative pressure phase time is between 1 and 2.5 hours; longer negative pressure phases may be needed for larger wounds, since short negative pressure times may lead to frequent need to exchange the solution-emptying container[80].

Choice of instillation solution

It is recognised that a number of solutions have been used for NPWT with instillation, including:

- Antibiotics, such as vancomycin, gentamycin, tobramycin, polymyxin B, bacitracin, neomycin
- Hypochlorite-based solutions (such as hypocholorous acid, sodium hypochlorite [superoxidised water HCOl], Dakin's solution (quarter strength), Dermacyn® [Oculus IS], Microcyn® [Oculus IS])
- Silver nitrate (0.5%)
- Biguanides (e.g. polyhexamethylene biguanide [Prontosan®, B Braun])
- Cationic solutions (e.g. octenidine 0.1% [octenillin®, Schulke])
- Acetic acid 1%
- Povidone-iodine (Betadine®)
- Normal saline

Recorded applications of NPWT with instillation refer to various types of solution, but most articles provide limited information on suggested instillation time, dwell time, or duration of the vacuum phase[58]. Evidence supports the following cycles based on solution type (including dwell time and cycles per day):

- 0.9% normal saline — mean duration of NPWT with instillation of 12 days; dwell time range of 5-60 minutes; 4 cycles per day[64;82-84]
- Polyhexanide — mean duration: 4-8 days, 0.02% or 0.04%; dwell time: 20 minutes, 4-8 cycles per day[67;75;58;85;60;84;86]
- Octenidine-based irrigation solution — mean duration: 4-8 days; dwell time: 5 minutes; 4-8 cycles per day[87]
- Dakin's solution — mean duration: 10 days, diluted 12.5%; dwell time: 10 minutes; 24 cycles the day[88;65]
- Superoxidised water — mean duration 4-8 days; dwell time: 5 minutes; 18 cycles per day[89;65]
- Acetic acid solution — mean duration 4-8 days, 1%; dwell time: 20 minutes; 4-8 cycles per day[58;90]

More work is needed to optimise range, dose and delivery of these agents, and it is important to evaluate the unique properties of each instillation solution to assess potential toxicity, efficacy, availability and cost. It is also suggested that fluid returned after therapy should be cultured for further study

Table 6 summarises the findings of a recent literature review on available irrigation solutions[58]

There is evidence to suggest that antiseptic solutions such as povidone-iodine, chlorhexidine and hydrogen oxide may be toxic to the total tissue and could prevent wound healing, with alternatives including warm water (32–37 degrees) and 0.5% and 1.0% taurolidine-Ringer solutions for debridement and 4% taurolidine gel for topical treatment of infection (although there were no RCTs for these applications meeting the selection criteria for this literature review)[58]. Indeed, evidence from various studies demonstrates that normal saline can achieve comparable outcomes to other solutions[98].

However, results of a retrospective case-control cohort study may dispute these findings. Patients treated with polyvinyl alcohol foam irrigated three times a day with a polyhexanide antiseptic solution (after surgical debridement) were compared with a control group who underwent surgical debridement, implantation of gentamicin polymethylmethacrylate beads, and received long-term intravenous antibiotics. The rate of infection recurrence in the instillation group was 3/30 (10%), compared with 55/93 (58.5%) of the controls ($p<0.0001$). In addition, patients treated with instillation had a shorter total duration of hospital stay and fewer surgical procedures compared with the controls (all $p<0.0001$)[67].

Since there is a lack of evidence from well-designed RCTs related to selection of an antiseptic agent for NPWT with instillation, it is important to carefully consider biocompatibility when making a choice of solution, taking into account all the available evidence on efficacy and tolerability, the type of wound, and the patient's condition[58]. In addition, there are few studies that compare different active substances, with most comparing an active substance with a control (NaCl or Ringer's solution); therefore, choice of antiseptic agents must be based on all available data.

In an era of multi-resistance to antibiotics, new strategies are certainly needed for infection control. Although dermatologists disagree regarding the use of topical antibiotics as instillation solutions, orthopaedic specialists routinely use topically applied solutions, such as gentamycin or vancomycin in PMMA cement. Despite this, there are no published recommendations or guidelines for their use, and as such, there is a need to collect further data in this area.

TABLE 6 | Findings of literature review on available irrigation solutions[58]

Reference	Comparators	Findings
Chang, 2006[91]	Sterile tap water vs. NaCl	Sterile tap water is equal to NaCl irrigation to cleanse contaminated acute wounds, including open fractures
Chang, 2006[91]	Soap or antibiotic rinses vs. NaCl	Washing with soap or an antibiotic rinse has shown no advantage over NaCl flushing
Chang, 2006[91]	Povidone-iodine vs. NaCl	Povidone-iodine has shown improved rates of infection prevention at the surgical site for spinal surgery compared with NaCl rinses
Chang, 2006[91]	Povidone-iodine vs. Dermacyn	Povidone-iodine has poor results compared with Dermacyn when applied for infection prevention on sternal wounds
Daeschlein G et al, 2007[92]	Polyhexamide vs. povidone-iodine and silver nitrate	Polyhexamide leads to faster wound healing compared with povidone-iodine and silver nitrate in mesh graft-treated burns
Moscati et al, 2007[93]	Tap water vs. saline solution	Tap water is less expensive, and just as safe and effective, than saline solution, with the incidence of infection the same or lower with tap water
Chisholm et al 1992[94]; Khan and Naqvi, 2010[95]; Watt et al, 2004[96]	Saline vs. diluted 1% povidone-iodine	No difference was seen between saline and diluted 1% povidone-iodine in terms of infection rates
Cartotto et al, 1996[97]	Tap water, saline	Tap water or a saline solution is recommended for irrigation or decontamination with burns

SECTION SUMMARY

- The optimal interface material should protect the surrounding skin, promote granulation, remain intact during therapy, and enhance fluid delivery and removal.
- When choosing an appropriate pressure setting, ensure nutritive perfusions of the tissue are considered.
- Amount of instillation fluid will depend on the size and shape of the wound, and should be determined by the clinician on the basis of when the foam seems visibly saturated.
- A balance should be reached between the length of dwell time of the instillation fluid and the length of time over which negative pressure is applied based on available evidence, taking into account the size of the wound.
- It is important to evaluate the unique properties of available instillation solutions to assess potential toxicity, efficacy, availability and cost. More work is needed to optimise range, dose and delivery of these solutions.

Summary

Over recent years, NPWT has revolutionised the advanced management of many wound types, and its successful use has prompted development of numerous new types of system. wThis document represents the views of an expert working group who met in November 2015. It presents principles and recommendations regarding the role of NPWT in the management of infected wounds and explores the potential for innovative NPWT systems to manage complex acute and chronic wounds.

It is important to recognise that challenges remain with regards to accurate diagnosis, and effective and appropriate treatment, of wound infection. There is a need to focus on building a strong evidence base for use of NPWT as an advanced treatment for complex wounds and as an adjunct for prevention and management of infection. Indeed, there may be value in a registry to document success and failures and share experiences, and to collect data from RCTs to help build the evidence base.

NPWT with instillation has the potential to be transformative in the management of wound infection, by use of effective topical treatments, although further evidence is needed to establish the optimal instillation solution, pressure level and cycle frequency. In an era where antibiotic stewardship is seen as one of grand challenges in healthcare, judicious use of such a treatment may constitute a significant step forward. Inappropriate use may exacerbate the problem of antimicrobial resistance or skin sensitisation, so developments should be monitored carefully.

PRINCIPLES OF BEST PRACTICE FOR USING NPWT

1. Conduct a thorough assessment of the patient and their wound – review the patient's history, any contraindications to NPWT, the setting where the device will be used, and the overall presentation of the wound:
   a. To ensure maximum success of NPWT, it is important to ensure accuracy of diagnosis and address all underlying or associated comorbidities that could inhibit the immune system and impact wound healing.
   b. A complete wound assessment, including location, size (e.g., area, volume, depth), base colour, amount and type of exudate, odour, and presence of oedema is necessary to determine the status of the wound and risk of bleeding.

2. Define the intended outcomes and select an indication-specific NPWT device, before establishing a timeline for care for each patient. Consider more advanced NPWT systems where relevant:
   a. Patients with closed incisions at risk of complications such as infection may benefit from ciNPT.
   b. Choice of NPWT with instillation should be based on the need for antisepsis or wound cleansing.

3. Carry out appropriate wound bed preparation prior to application to ensure optimal outcomes:
   a. Debride the wound to remove any dead or devitalised tissue. It may also be appropriate to cleanse the wound thoroughly (according to local practices) to reduce bioburden.
   b. Consider use of a light layer of a skin barrier product to protect the surrounding skin (although this may not be necessary in every case).

4. Choose the most appropriate type of NPWT in the most appropriate healthcare setting based on the patient's need for monitoring and wound care (i.e. portable systems can be used in the community, or NPWT with instillation in a hospital environment), and apply according to manufacturer's instructions.

5. Monitor progress and discontinue when goals of treatment have been reached. If no improvement is seen, review the treatment plan.

6. Appropriate training should be given to healthcare providers on how to apply the NPWT device, including its indications and contraindications, and recognition and management of potential complications.

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