

# EWMA DOCUMENT: NEGATIVE PRESSURE WOUND THERAPY

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OVERVIEW,  
CHALLENGES  
AND  
PERSPECTIVES



**Jan Apelqvist**,<sup>1,2</sup> (editor) MD, PhD, Associate Professor  
**Christian Willy**,<sup>3</sup> (co-editor) MD, PhD, Professor of Surgery  
**Ann-Mari Fagerdahl**,<sup>4</sup> RN, CNOR, PhD  
**Marco Fraccalvieri**,<sup>5</sup> MD  
**Malin Malmsjö**,<sup>6</sup> MD, PhD, Professor  
**Alberto Piaggese**,<sup>7</sup> MD, Professor of Endocrinology  
**Astrid Probst**,<sup>8</sup> RN  
**Peter Vowden**,<sup>9</sup> MD, FRCS, Professor

1. Department of Endocrinology, University Hospital of Malmö, 205 02 Malmö, Sweden

2. Division for Clinical Sciences, University of Lund, 221 00 Lund, Sweden

3. Department of Trauma & Orthopedic Surgery, Septic & Reconstructive Surgery, Bundeswehr Hospital Berlin, Research and Treatment Center for Complex Combat Injuries, Federal Armed Forces of Germany, 10115 Berlin, Germany

4. Department of Clinical Science and Education, Karolinska Institutet, and Wound Centre, Södersjukhuset AB, SE-118 83 Stockholm, Sweden.

5. Plastic Surgery Unit, ASO Città della Salute e della Scienza of Turin, University of Turin, 10100 Turin, Italy

6. Clinical Sciences, Lund University, Lund, Sweden.

7. Department of Endocrinology and Metabolism, Pisa University Hospital, 56125 Pisa, Italy

8. Kreiskliniken Reutlingen GmbH, 72764 Reutlingen, Germany

9. Faculty of Life Sciences, University of Bradford, and Honorary Consultant Vascular Surgeon, Bradford Royal Infirmary, Duckworth Lane, Bradford, BD9 6RJ, United Kingdom

Editorial support and coordination: **Niels Fibæk Bertel**, EWMA Secretariat

Corresponding author: **Jan Apelqvist**, jan.apelqvist@skane.se

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Tel: +44 (0)20 7738 5454 Email: [anthony.kerr@markallengroup.com](mailto:anthony.kerr@markallengroup.com) Web: [www.markallengroup.com](http://www.markallengroup.com)

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# Abbreviations

- ACS: Abdominal compartment syndrome
- ABRA: Abdominal re-approximation anchor system
- ADR: Acellular dermal replacement
- bFGF: Basic fibroblast growth factor
- BMI: Body mass index
- Cdc42: Cell division control protein 42
- ciNPT: Closed incision negative pressure therapy
- CI: Confidence interval
- CABG: Coronary artery bypass grafting
- CRP: C-reactive protein
- DRG: Diagnosis related groups
- DSWIs: Deep sternal wound infections
- DFUs: Diabetic foot ulcers
- ECF: Enterocutaneous fistula
- EPUAP: European Pressure Ulcers Advisory Panel
- EWMA: European Wound Management Association
- ERK: Extracellular signal-regulated kinase
- FDA: US Food and Drug Administration
- FGF-2: Fibroblast growth factor-2
- HR: Hazard ratio
- HIF: Hypoxia-induced factor
- IE: Immediate early
- IM: Intermittent mode
- ICU: Intensive care unit
- LC-MS/MS: Liquid chromatography mass spectrometry
- LUs: Leg ulcers
- MRSA: Meticillin-resistant *Staphylococcus aureus*
- NBC: Nucleated blood cells
- NICE: National Institute for Health and Care Excellence
- NPWT: Negative pressure wounds therapy
- NPWTi: NPWT with instillation
- NO: Nitric oxide
- OA: Open abdomen
- PDGF: Platelet derived growth factor
- PHMB: Polyhexamethylene biguanide

- PVA: Polyvinyl-alcohol
- PU: Pressure ulcer
- PHI: Private Health Insurance
- QoL: Quality-of-life
- RCTs: Randomised controlled trials
- RR: Relative risk
- SHI: Statutory health insurance
- SSD Silver sulfadiazine treatment
- SSI: Surgical site infections
- SWD: Surgical wound dehiscence
- SDR: Synthetic dermal replacement
- TAC: Temporary abdominal closure
- VEGF: Vascular endothelial growth factor
- WBP: Wound bed preparation
- VEC: vascular endothelial cell

# I. Introduction

Since its introduction in clinical practice in the early 1990's negative pressure wound therapy (NPWT) has become widely used in the management of complex wounds in both inpatient and outpatient care.<sup>1</sup> NPWT has been described as an effective treatment for wounds of many different aetiologies<sup>2,3</sup> and suggested as a gold standard for treatment of wounds such as open abdominal wounds,<sup>4-6</sup> dehiscence sternal wounds following cardiac surgery<sup>7,8</sup> and as a valuable agent in complex non-healing wounds.<sup>9,10</sup> Increasingly, NPWT is being applied in the primary and home-care setting, where it is described as having the potential to improve the efficacy of wound management and help reduce the reliance on hospital-based care.<sup>11</sup>

While the potential of NPWT is promising and the clinical use of the treatment is widespread, high-level evidence of its effectiveness and economic benefits remain sparse.<sup>12-14</sup>

The ongoing controversy regarding high-level evidence in wound care in general is well known. There is a consensus that clinical practice should be evidence-based, which can be difficult to achieve due to confusion about the value of the various approaches to wound management; however, we have to rely on the best available evidence. The need to review wound strategies and treatments in order to reduce the burden of care in an efficient way is urgent. If patients at risk of delayed wound healing are identified earlier and aggressive interventions are taken before the wound deteriorates and complications occur, both

patient morbidity and health-care costs can be significantly reduced.

There is further a fundamental confusion over the best way to evaluate the effectiveness of interventions in this complex patient population. This is illustrated by reviews of the value of various treatment strategies for non-healing wounds, which have highlighted methodological inconsistencies in primary research. This situation is confounded by differences in the advice given by regulatory and reimbursement bodies in various countries regarding both study design and the ways in which results are interpreted.

In response to this confusion, the European Wound Management Association (EWMA) has been publishing a number of interdisciplinary documents<sup>15-19</sup> with the intention of highlighting:

- The nature and extent of the problem for wound management: from the clinical perspective as well as that of care givers and the patients
- Evidence-based practice as an integration of clinical expertise with the best available clinical evidence from systematic research
- The nature and extent of the problem for wound management: from the policy maker and health-care system perspectives

The controversy regarding the value of various approaches to wound management and care is illustrated by the case of NPWT, synonymous



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with topical negative pressure or vacuum therapy and cited as branded VAC (vacuum-assisted closure) therapy. This is a mode of therapy used to encourage wound healing. It is used as a primary treatment of chronic wounds, in complex acute wounds and as an adjunct for temporary closure and wound bed preparation preceding surgical procedures such as skin grafts and flap surgery.

## Aim

An increasing number of papers on the effect of NPWT are being published. However, due to the low evidence level the treatment remains controversial from the policy maker and health-care system's points of view—particularly with regard to evidence-based medicine.

In response EWMA has established an interdisciplinary working group to describe the present knowledge with regard to NPWT

and provide overview of its implications for organisation of care, documentation, communication, patient safety, and health economic aspects.

These goals will be achieved by the following:

1. Present the rational and scientific support for each delivered statement
2. Uncover controversies and issues related to the use of NPWT in wound management
3. Implications of implementing NPWT as a treatment strategy in the health-care system
4. Provide information and offer perspectives of NPWT from the viewpoints of health-care staff, policy makers, politicians, industry, patients and hospital administrators who are indirectly or directly involved in wound management.

## 2. Methodology and terminology

**O**ur methodology for this document comprises a general literature review supplemented with individual searches on the specific topics along with the addition of the authors' clinical expertise. Most research with regard to wound healing and NPWT has been related to acute wounds and to a lesser extent chronic/problematic/non-healing wounds.<sup>12,13,15,20,21</sup>

The opinions stated in this document have been reached by a consensus of the authors involved, based on evidence-based literature, published research articles and clinical experience and these opinions have been externally reviewed. This paper is not purely evidence-based or an evaluation of existing products, as this would compromise the primary objective.

Since the authors are residents of Europe and EWMA is a European association, the document will particularly take European patients and health-care systems into consideration. The document will focus on the human (clinical) perspective; however, animal related studies will be mentioned when applicable.

### Search history and document development

As a general conclusion with regards to the literature search we acknowledge that more high-level evidence is needed to further support the content of this document. However, until this has been provided, we have to rely on existing information and experience.

Each chapter of the document has been divided between the authors, who have provided feedback in an edited draft. This process has been repeated several times; the group edited the final document and all authors agreed on all controversies, statements, and discussions. The final draft was sent to resource persons, EWMA council members, and supporters to comment on the draft in an internal validation process.

Besides an initial literature search, a specific literature search was made with regard to the study design, endpoints, and outcomes in comparative/randomised controlled trials (RCTs) of NPWT.

### Terminology

The term NPWT refers to a controlled negative pressure (sub-atmospheric) system that is applied topically onto the wound. The wound is filled with a porous material (wound filler) and hermetically sealed with an airtight adhesive polyurethane drape. A drain connects the wound filler to the vacuum source that delivers a negative pressure. The suction is propagated from the vacuum source to the wound bed, leading to a negative pressure in the filler and removal of exudate. Two more recent modifications of NPWT are also discussed:

- 'NPWT with instillation' (NPWTi), NPWT with a repeated computer-controlled retrograde instillation mostly of an antiseptic or antibiotic substance as well as saline into the sealed wound.
- Same applies for the closed incision negative pressure therapy (ciNPT) when NPWT is applied directly to a closed surgical wound (ciNPT).

# 3. The principles of NPWT

**N**PWT can be regarded as an established wound care method in routine clinical use since the mid to late 1990's. Stated simply, the method consists of application of negative pressure (usually  $-75$  to  $-125$  mmHg) to foam that has been placed inside the wound. Immediate sealing of the wound with an airtight adhesive drape prevents subsequent entry of air from the environment, hence the term 'vacuum sealing'.

In the following sections the principle of conventional NPWT and the modifications NPWTi (1996) and cNPWT (2005), will be presented.

## Short history

In 1979, a suction and irrigation system for the treatment of wounds was described in a Russian publication.<sup>22</sup> In 1992, in Germany, patients with exposed fracture were treated with a negative pressure system. Initially, the loss of substance was filled with a polyvinyl-alcohol (PVA) foam, (later there was a change towards more polyurethane), to which drainage tubes were connected all wrapped in a transparent film. The drainage pipes were connected to a suction device, and a negative pressure was applied.<sup>23</sup> This system allowed the efficient cleansing of the wound and a significant proliferation of granulation tissue. In 1997, the work of Argenta and Morykwas<sup>24</sup> validated NPWT in an animal (pig) model and subsequently on patients with ulcerative lesions.<sup>25</sup> These studies reported the positive effect of the negative pressure on blood flow in the wound and in the adjacent tissue (via Doppler evaluation), on the rate of granulation tissue formation and on the reduction of bacterial load.<sup>24</sup> In

2000, Joseph et al.<sup>26</sup> and McCallon et al.<sup>27</sup> compared the efficacy of NPWT with standard methods of treatment of wounds, showing a statistically significant reduction in the size of the lesions and the time to healing in the group receiving NPWT. The first wound filler to be widely available for NPWT was the polyurethane foam.<sup>24</sup> Gauze appeared in an article on NPWT by Chariker in 1989.<sup>28</sup> In 2007, cotton gauze preimpregnated with 0.2% antiseptic polyhexamethylene biguanide (PHMB), was introduced as a commercially available product. An important development in the field of NPWT is the introduction of new materials for wound fillers.

## Functional principle of NPWT

The principle of NPWT involves extending the usually narrowly defined suction effect of drainage across the entire area of the wound cavity or surface using an open-pore filler that has been fitted to the contours of the wound. To prevent air from being sucked in from the external environment, the wound and the filler that rests inside or upon the wound are hermetically sealed with an airtight adhesive polyurethane drape that is permeable to water vapour, transparent, and bacteria proof. A connection pad is then applied over a small hole that has been made in the drape and connected to a vacuum source by means of a tube (Fig 1).

## Example of application

A patient case is presented to illustrate the individual steps involved showing the hygienic and comfortable management of an infected and unstable sternal wound in a 73-year-old patient (Fig 2).

## Mechanism of action of NPWT

The following effects on wound healing and the affected tissue, resulting from applied suction that acts evenly on the entire wound surface, are considered to be the primary clinically significant benefits of NPWT.<sup>23,25,29-35</sup>

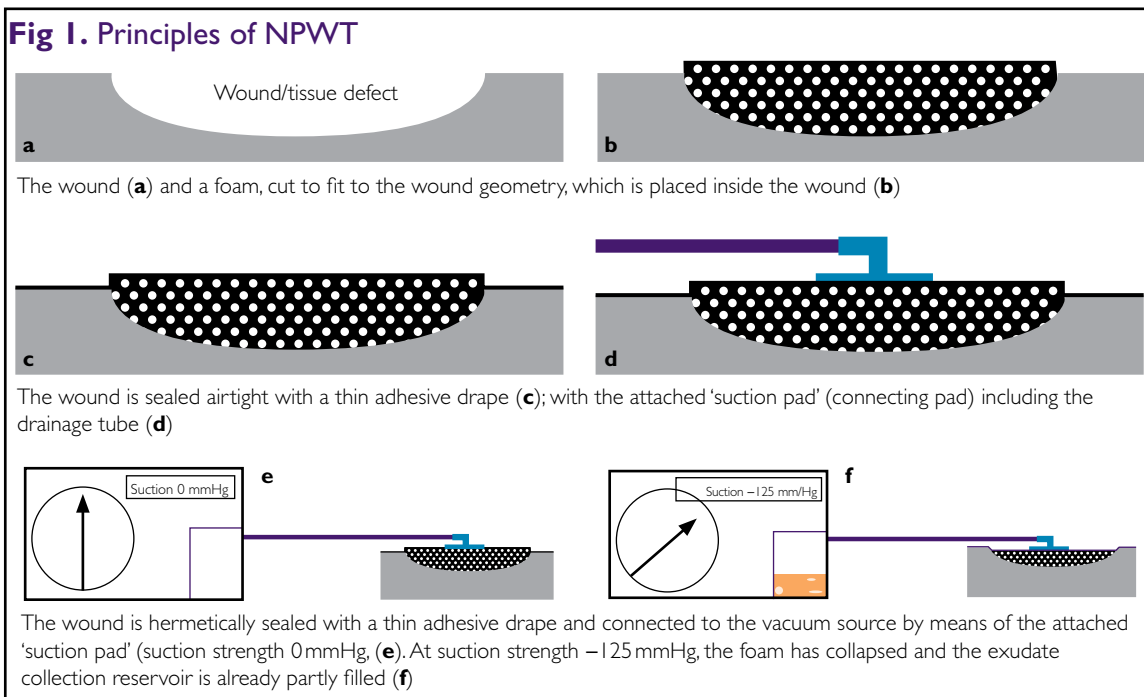
### Effect on the wound

- Reduction of the wound area due to negative pressure acting on the foam, pulls together the edges of the wound (wound retraction)
- Stimulation of granulation tissue formation in an optimally moist wound environment; in several situations even over bradytrophic tissue such as tendons and bone NPWT was able to stimulate granulation tissue formation
- Continuation of effective mechanical wound cleansing (removal of small tissue debris by suction)

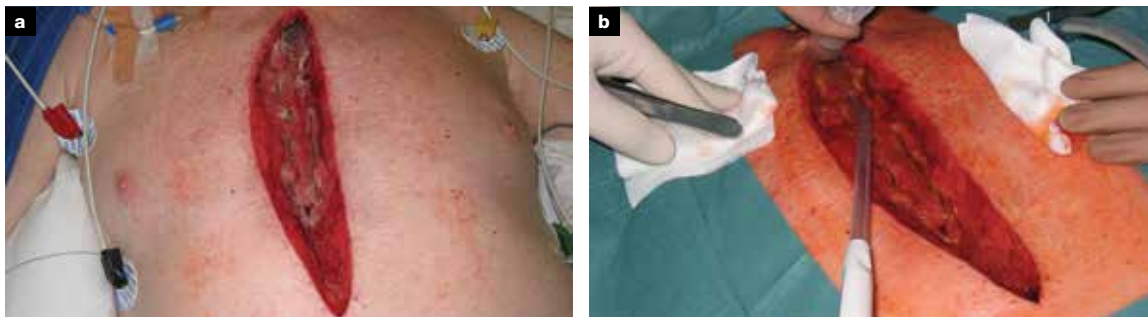
- Effective biochemical reduction of the fluid concentration of wound healing-impairing proteases (such as elastase)—in the first days
- Reliable, continuous removal of wound exudate (and, consequently, fewer dressing changes) within a closed system
- Pressure-related reduction of interstitial oedema with consecutive improvement of microcirculation, stimulation of blood flow and oxygenation.

### Handling

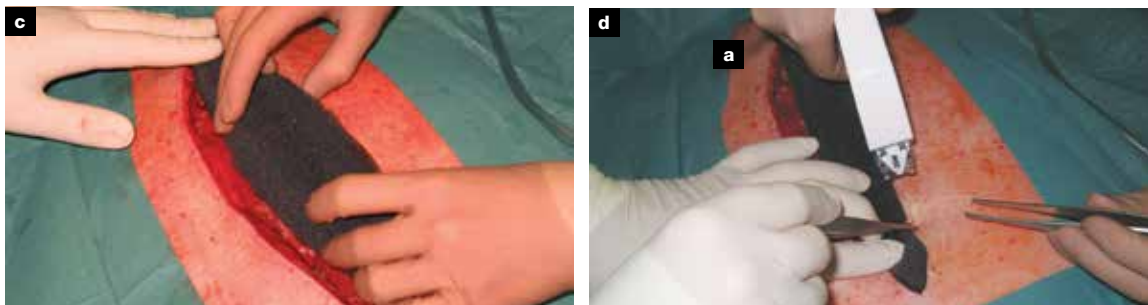
- Hygienic wound closure—bacteria proof wound dressing for sealing the wound so no external bacteria can enter the wound and the patient's own wound bacteria are not spread. This is particularly important in the event of contamination with problematic bacteria, as in patients with meticillin-resistant *Staphylococcus*



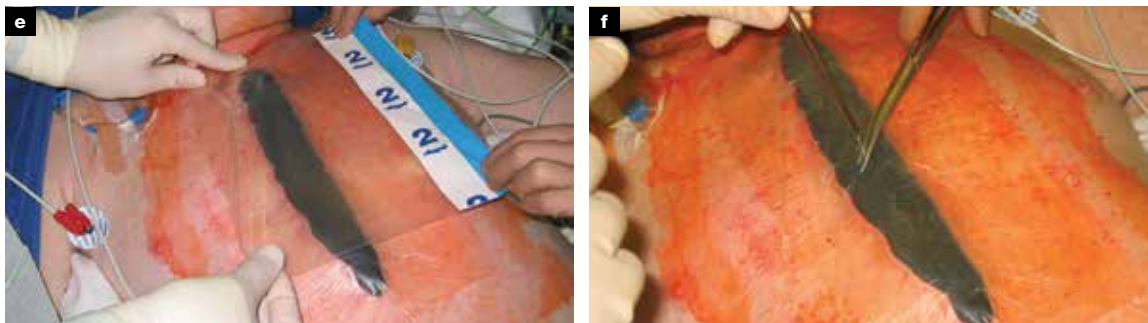
**Fig 2.** Example of application



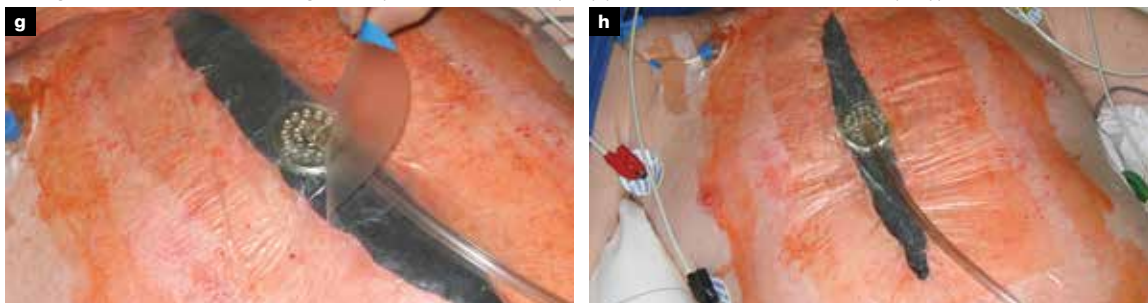
Infected sternal wound, unstable sternum after sternotomy, fibrinous membranes and necrosis, particularly in the cranial part of the wound (a). Debridement and irrigation of the wound (b)



The foam is fitted to the shape of the wound (black polyurethane foam) (c). Fixation of the foam to the lateral wound edges with skin staples (this can be done with a skin suture or without any fixation) (d)



Sealing of the wound with an airtight transparent adhesive drape (e). A small hole is cut into the drape (f)



The connecting pad is applied onto this hole (g). Wound after connection of the vacuum source at  $-125$  mmHg (h). Compared with the initial finding (g), there is a distinct narrowing of the wound due to the 'shrinking' of the foam caused by suction

*aureus* (MRSA)-infected wounds. Thus, it also reduces the risk of cross-infections and development of resistance within the hospital

- Transparent dressing permits continuous clinical monitoring of the surrounding skin through the film with which the wound has been sealed
- Odourless and hygienic dressing technique; constant seeping through the dressing onto the patient's clothing and bedding can be avoided, reducing demands on the nursing staff
- Reduction in the number of required dressing changes (only necessary every two to three days), which reduces nursing time requirements, particularly in patients with exudating wounds.

### Patient comfort

- Easy and early patient mobilisation
- Visually appealing dressing method due to clean, exudate-free dressing conditions even during mobilisation.

## Functional principle of NPWTi

Instillation therapy is a modification of conventional NPWT for the complementary treatment of acute and chronic wound infections after initial surgery.

Instillation therapy can be performed according to the method of Fleischmann et al. to deal with any residual contamination of the wound.<sup>35–37</sup> This modification involves the retrograde instillation of an antiseptic or antibiotic substance, such as pyrrolidinone homopolymer compound with iodine or octenidine dihydrochloride, into the sealed wound. Instillation therapy has been used clinically since 1996. Since then, several refinements in equipment have provided the option of automatically controlled instillation therapy. This permits constantly controlled instillation, for

example every three hours, without burdening the patient or nursing staff. Using today's computer-controlled programmable therapy units it is possible to automatically control the instillation therapy (amount of fluid, duration of instillation, time for which the substance is allowed to take effect, frequency of the therapy, etc.). NPWTi has been successfully used for the treatment of acute wound infections after surgical wound debridement.<sup>35,37–41</sup> Nowadays, some authors suggest that non-infected wounds might also show a benefit in healing when treated by NPWTi using saline solutions in comparison with conventional NPWT or standard moist wound treatment.<sup>42,43</sup>

## Mechanism of action of NPWTi

Instillation therapy is performed during NPWT by instilling the desired solution into the foam via a dedicated tube system and then, after a set time during which the instillation is left to take effect with no suction applied, removing the solution by suction and continuation of the actual NPWT. In principle, this alternation between NPWT and instillation periods can be repeated as often as desired. In fact, it is suggested that the instillation should be performed several times a day for sufficient effect according to a controlled time sequence. As an example, for an antimicrobial effect:

- Instillation period of the saline/antiseptic/topical antibiotic solution approximately 10–30 seconds
- Dwelling period (depending on the time the solution needs to be effective, such as 20 minutes)
- Suction period, such as 2–3 hours.

## Functional principle of ciNPWT

Traditionally, surgeons have closed surgical incisions with primary intention using sutures, staples, tissue

adhesives, paper tape, or a combination of these methods. Recently, surgeons are using negative pressure therapy immediately postoperatively over closed incisions in a variety of clinical settings to prevent surgical site infections (SSIs). 'Closed incision negative pressure therapy' refers to any type of NPWT over closed incisions. Since 2006, numerous published studies have reported improved incisional outcomes using ciNPT across surgical disciplines.

## Lack of mechanism of action ciNPT

ciNPT appears to manage the surgical incision by reducing incision line tension, decreasing oedema, and providing an airtight seal, beneficial in preventing incision complications.

## Differences in mechanism of action in ciNPT and NPWT

It is important to recognise that clear differences exist between the mechanism of action of ciNPT and NPWT on open wounds. The evidence for ciNPT supports the reduction of lateral tension and haematoma or seroma, coupled with an acceleration of the elimination of tissue oedema.

Conventional NPWT on open wounds causes a mechanical stress of the wound edges that alters tissue perfusion, resulting in angiogenesis and the formation of granulation tissue. To the knowledge of the authors, no such evidence exists for ciNPT, in fact, the literature shows there is no altered perfusion.<sup>44</sup> However, ciNPT is reported to have a good clinical outcome.

# 4. Review of the literature evidence on NPWT

**M**any national and international peer-reviewed articles on the subject of NPWT have appeared in the medical literature and it has been the subject of congresses worldwide. An analysis of the literature shows that a large proportion of the publications on NPWT in all surgical disciplines are congress reports, opinions and experience reports, which were not submitted to a formal peer-review process. The following analysis of the available literature dealing with NPWT provides an overview of the peer-reviewed literature published to date. Attention is directed to the following:

- Development of the annual number of publications
- Language area where the publications originated
- Proportion of studies on the pathophysiological background of NPWT
- ‘Quality’ of the studies under the criteria of evidence-based medicine.

## Literature search

In order to identify publications that satisfy at least a minimum quality standard, only papers that met the following criteria were selected: published in a journal with clearly defined author guidelines and a defined description of the peer-review procedure. The analysis was based on the results of a computerised MEDLINE (with PubMed) search as well as an extensive hand search, in which the references of all available citations were also assessed

(we used the ‘snowball’ method and searched the references of the self-researched publications). Irrespective of the evidence of the publications (all languages), the search involved randomised clinical and experimental studies, systematic and non-systematic reviews, meta-analyses, expert opinions, case reports, experimental papers (animal and human studies) and result reports of consensus conferences. The universally valid biometric requirements—such as suitability of the primary endpoints for the statement, sufficient number of cases, representativeness of the study population, relevant dosages and significance of the results—were taken into account for an assessment of the studies. However, where necessary, the assessment also considered the particular nature of the question addressed. In these cases, the assessment criteria played a secondary role. It should be mentioned, that for some of the questions addressed a search was also carried out for relevant theses, unpublished research reports and congress minutes.

## Search period and search keywords

The search covered papers published in the period up to 31 December 2015. The keywords included (‘all fields’-search): ‘negative pressure wound therapy’ ‘NPWT’, ‘vacuum assisted closure’, ‘VAC therapy’, ‘V.A.C. therapy’, ‘vacuum dressing’, ‘topical negative pressure therapy’, ‘TNP therapy’ (the abbreviation of topical negative pressure), ‘sealed surface wound suction’, ‘vacuum sealing therapy’, ‘subatmospheric pressure therapy’, foam suction dressing’. (See Table, appendix 1).



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## Results

### Development in the number of annual publications

We identified 3287 publications, published in 685 different journals between 1990–31 December 2015 (see appendix 2, 3 and 4).

### NPWT and evidence-based medicine

#### Criteria of evidence-based medicine

The evaluation of the relevant literature was based on the classification of the Oxford Centre for Evidence-Based Medicine (CEBM).<sup>45</sup>

Evaluation based on CEBM shows that over 85% are case series or case reports, evidence levels 4 and 5.

This leaves ~200 published articles with an evidence level higher than 4 (table x, appendix 5). There were 271 comparative studies. Continuing this selection process for only RCTs (n=76) being focused on primary endpoint analysis using for patient's benefit relevant endpoints:

- Time to definitive wound closure
- Time to prepare for 'ready for surgery'
- Graft take rate
- Graft quality
- Delayed primary fascial closure (closure of open abdomen)
- Rate of surgical site infections
- Mortality

There were 27 RTCs remaining (Tables, appendix 3 and 6).

Prospective randomised studies in surgery are rare.<sup>46,47</sup> In trauma surgery, the rate is approximately 3% of all publications. In this NPWT context there is remarkable disproportion between the number of systematic reviews (n=68) and the amount of randomised studies assessing the clinical usefulness of NPWT in comparison with standard procedures (n=57). Thus there are more studies searching for evidence in the literature than studies creating the proof of effectiveness/efficiency of NPWT in the clinical routine!

One reason for this situation is a gap between clinical practice, on the one hand, and scientific findings and evidence-based medicine requirements, on the other. Clinicians who use a new treatment method and find it effective will usually publish case reports or observational studies reflecting the treatment success on the basis of their experiences. They will focus attention on an exact description of the method and potential risks and benefits. Evidence-based medicine principles will play only a minor role in their work. Only very rarely will clinicians find the time and support to be able to conduct an RCT with all the additional tasks involved and at the same time perform their daily work. The fact that many 'renowned' journals have published these articles reflects the importance NPWT even at this relatively low evidence level. It is thus explainable and understandable that approximately 66% of the international peer-reviewed literature on NPWT consists of case descriptions.

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#### Particularities of NPWT and NPWTi

NPWTi is a further development and modification of conventional NPWT for the complementary treatment of acute and chronic wound infections after initial surgery. NPWTi has been used clinically since 1996, and between and during 1999–2013 several refinements in equipment have provided the option of automatically controlled instillation therapy. The first publications date from 1998 (Fleischmann et al).<sup>23</sup> There are currently 105 peer-reviewed articles that have been published on the subject of NPWT in combination with instillation (keywords: ‘instillation’, ‘instill’, ‘Irrigation’; as of 31 December 2015, see figure, appendix 7) and seven studies comparing NPWTi with NPWT or standard therapies, however, there are no RCTs. NPWTi, the modifications and the indications are explained in more detail on page 54 (chapter 5, section on NPWTi).

#### Particularities of ciNPT

There is a rapidly emerging literature on the preventive effect of ciNPT in SSI. Initiated and confirmed first with An RCT in orthopaedic trauma surgery,<sup>48</sup> studies in abdominal, plastic, vascular and cardiothoracic surgery with good effect on SSI rate reduction have been reported. There are currently 116 peer-reviewed articles that have been published on the subject of NPWT in combination with closed incisions (keywords: ‘closed incision management’, ‘active incision management’, ‘prevention’, ‘prophylaxis’; as of 31 December 2015, see figure, appendix 7) and 27 studies comparing NPWTi with standard incisional wound management (RCTs n=8). ciNPT, the modifications and the indications are explained in more detail on page 56 (Chapter 5, section on ciNPT)

# 5. Treatment

## Development of the range of indications: NPWT 1990–2015

The first clinical experiences with NPWT as it is used today occur from 1987 onwards when acute traumatic soft tissue defects and acute and septic wounds were treated with this method. Publications followed in the early 1990's. Very soon, the range of indications was extended to chronic wounds such as leg ulcers (LUs), decubitus ulcers; see also flowchart, appendix 8). Since 2000, there has been a marked extension of the range of indications including severe dermatological syndromes and problematic wounds in vascular surgery as well as an increasing use in plastic surgery. From then on, the spectrum of indications has been continuously expanded so that NPWT is today used in almost all areas of surgery.

There are more than 100 indications identified for NPWT. In visceral surgery, entero- and lymphocutaneous fistulas and open abdomens are treated with NPWT. In trauma surgery, the range of indications has been extended to implant infections in the fields of endoprosthetics and spinal surgery, while burns (burns of the hand, fixation of skin substitutes) are found to be an ideal indication for NPWT. In visceral and thoracic surgery, NPWT is not only used on the body surface for the management of septic wounds or defect regions but also when there are problematic conditions deep in the body cavity (bronchial stump insufficiency, pancreatic trauma). NPWT is now used in extreme age (newborn, very old

age), under clinically difficult situations (life-threatening abdominal sepsis) and high-risk situations such as long-term infections, to prevent complications (e.g. ciNPT - see page 56) and is based on newer technologies, such as computer-assistance, small hand-held and mechanically driven devices as well as NPWT combined with instillation (NPWTi – see page 53)

## Goals of the treatment and the scientific background

Mechanism of action:

NPWT on open wounds

NPWT acts in different ways to promote wound healing. The wound is subject to suction pressure that is propagated through the wound filler to the wound bed. This suction drains exudate from the wound and creates a mechanical force in the wound edges that result in an altered tissue perfusion, angiogenesis and the formation of granulation tissue. Some of the mechanisms of action have been demonstrated experimentally and clinically. The effects can be summarised as follows:

- Isolating the wound from infection of external origin
- Creating a moist wound environment
- Pressure transmission and removal of exudate
- Removal of oedema

- Mechanical stress of the wound edges
- Altered blood perfusion
- Angiogenesis and the formation of granulation tissue

NPWT isolates the wound and prevents it from being infected by the external environment. NPWT also involves sealing the wound with an airtight drape that will create a moist wound environment.

The mechanisms of action of the combination of NPWT and instillation and the special mechanisms of ciNPT will be described in chapter 5 page 53–60.

### Creating a moist wound environment and removal of exudate

A moist environment is vital in wound healing as it facilitates the re-epithelialisation process. However, in an overly moist wound, exudate may cause infection and maceration, leading to damage to the wound edge. Removal of exudate is important to prevent the accumulation of necrotic tissue and slough that tend to continually accumulate in wounds and alter the biochemical and cellular environment.<sup>49</sup> Stagnant wound fluid may also increase the risk of abscesses. The accumulation of necrotic tissue or slough in a wound promotes bacterial colonisation and hinders repair of the wound. NPWT balances these effects, providing a moist wound environment while removing excess fluid. Several studies have shown that NPWT removes exudate.<sup>24,25,50</sup>

### Removal of oedema

Oedema causes increased pressure on the wound tissue, which in turn compromises the microvascular blood flow, reducing the inflow of nutrients and oxygen. This reduces resistance to infections and inhibits healing, thus, in order to facilitate wound healing, it is important to reduce tissue oedema.

NPWT causes compression of the tissue closest to the surface of the wound, which is believed to reduce interstitial oedema.<sup>51,52</sup> There are few studies but there is widespread agreement among clinicians that NPWT eliminates tissue oedema. However, there are only a handful of studies that have directly measured this effect,<sup>24,25,53</sup> NPWT resulted in increased perfusion in patients with bilateral hand burns and it was concluded that oedema was reduced.<sup>54</sup> In an experimental study on the pig septic open abdomen, it was shown that the NPWT-treated pigs had less tissue oedema than those treated by passive drainage.<sup>55</sup> High-frequency ultrasound has been used to quantify reduction of oedema in the periwound tissue in a small group of pressure ulcer (PU) patients on commencement of NPWT.<sup>56</sup> Most probably, oedema and exudate are reduced both directly through mechanical removal of excess fluid, and indirectly through altered microcirculation.

### Mechanical effects on wound edges

NPWT mechanically stimulates the wound bed,<sup>57,58</sup> and produces a suction pressure on the wound edges that will push onto the wound and contract it.<sup>24,25,50</sup> The mechanical effects lead to tissue remodelling that may facilitate wound closure. It also has been found that the wound tissue and the filler material interact on a microscopic level to micro deform the tissue. These mechanical deformations<sup>58–62</sup> lead to a number of biochemical reactions and gene transcriptions. The wound bed is drawn into the pores of the foam or inbetween the threads of the gauze.<sup>58</sup> These mechanical effects affect the cytoskeleton of the cells and initiate a cascade of biological reactions that may accelerate the formation of granulation tissue and subsequent wound healing.

The mechanotransductive stimulus on the wound bed that is exerted by the foam under suction is regarded as an important effect of NPWT.<sup>24,63–67</sup> Mechanical tissue deformation stimulates the expression of angiogenic growth factors and

receptors, such as vascular endothelial growth factor (VEGF), VEGF receptors and the angiopoietin system receptors.<sup>59,61,68-73</sup> *In vitro* studies have shown that the stretching of endothelial cells stimulates blood vessel formation.<sup>74,75</sup>

The frequently cited explanation of the mechanical effects of NPWT is based on the reviews by Ingber,<sup>76</sup> which describes the current state of knowledge on the transduction of physical forces into biochemical responses on a cellular level. The conceptual model derived from these data describes how external forces, such as subatmospheric pressure, act on the cell through the extracellular matrix by means of transmembrane bridges (membrane molecules such as the integrins), causing the release of intracellular second messengers. According to the model, these messengers lead to the immediate activation of immediate early (IE) genes, followed by matrix molecule synthesis and cell proliferation, as described in the papers by Sadoshima et al., Vandeburgh et al. and Bauduin-Legros et al.<sup>65,77-80</sup>

Mechanical stress also promotes the production of extracellular matrix components such as collagen, elastin, proteoglycans and glycosaminoglycans.<sup>61,73,81</sup> A murine study revealed a significant increase in dermal and epidermal nerve fibre densities in wounds treated with NPWT, indicating that the treatment may promote nerve production.<sup>82</sup> It may be important to control the state of stress and strain in the wound bed in order to affect the wound healing effects of NPWT.<sup>76,83-85</sup>

The studies of Ingber do not investigate the effects of NPWT on the cell. The application of the study results about stretching cell models is merely based on the assumption that NPWT also induces a stretching stimulus. Against the background of the diversity of cell responses to mechanical stimuli moving in the same direction, as mentioned by Sumpio, such a conclusion by analogy may only

be drawn very cautiously, if at all.<sup>66</sup> Also, it has not been proven to date that NPWT produces a pure stretching stimulus. Because of the filler architecture, it must rather be assumed that positive pressure values (on the pore wall resting on the tissue) and negative pressure values (in the region of the actual pore) are generated at the same time. To date, there are no studies on the spatial pressure distribution in the mm and  $\mu\text{m}$  ranges. In any case, when developing a concept of the principle of action of NPWT, one cannot work on the assumption that there is only one single stretching stimulus on cells. Instead of only one type of force acting on the cells, it is much more likely that pressure and/or shear stress (tangential force vector) and/or stretching forces act on the cells.

A deeper understanding of the heterogeneity of the mechanical forces acting on the cells of the filler/wound interface is conveyed by Saxena and Orgill.<sup>58</sup> In a computer simulation, they calculated the stretching stimulus that acts on the individual cells in the region of the foam pore wall and the foam pore space. The verification by histological examination revealed that the calculated results were valid. They were able to demonstrate that the cells in the region of the pore wall are 'squeezed' and the cells in the immediate vicinity of the pore wall are stretched greatly, while the cells in the pore space are stretched by approximately 5–20%. The authors explain that chemical stimuli such as soluble growth factors and the attachment to extracellular matrix proteins alone are not sufficient for the proliferation of cells, but that there must also be a mechanical context, which is usually associated with varying states of isometric tension of the cells. Furthermore, this state usually no longer exists in wounds but NPWT can compensate for this lack of mechanical stimuli. They refer to the literature in which stretching stimuli indeed had a proliferative effect.<sup>80,86,87</sup> In their model, they actually calculated stretching stimuli, as an effect of NPWT, of a magnitude

(5–20%), which had been found to be favourable in other studies. They did not discuss, that according to their calculations, individual cells experience stretching stimuli of over 110%, while other cells are compressed substantially. Assuming that in a cross-section of the pore, only 60% of the cells actually experience a stretching stimulus of 5–20%, this means that only one-third of all cells within the wound (area= $\pi r^2$ ) experience a favourable effect. This was not discussed.

It is necessary to consider that wounds are not simple single-phase linear elastic layers. As Lohman et al. discussed, this model obfuscates the role of fluid shear stresses and electrokinetic streaming potentials (movement of ions in solution) in stimulating responses. Mechanical deformation by external NPWT will also result in fluid flow within the interstices of the matrix.<sup>88</sup> Using NPWT, there are stretching, shearing and electromagnetic effects, probably with certain differences between continuous and intermittent therapy.

#### NPWT induced change in perfusion

Morykwas and co-workers found that continuous NPWT application of suction resulted in an average increase in new granulation tissue formation of approximately 60%, significantly increased compared to controls (moist wound management).<sup>24,89</sup> The research group reported that there was no positive effect on perfusion when a continuous suction of –125 mmHg was applied. After an initial increase in perfusion, the increased blood flow decreased permanently to baseline levels or even below baseline after only 10 minutes, reaching a state of normo- or hypoperfusion. Based on these results, they suggested that NPWT increases perfusion in the wound, contributing to wound healing—a conclusion that has been cited in almost every subsequent publication. This raises the question: Does hypo- or hyperperfusion of the wound tissue occur during NPWT?

Laser Doppler flow measurements were performed in other studies.<sup>90–93</sup> Although there are some inconsistencies, it still appears possible to derive a general hypothesis regarding the perfusion situation during NPWT. While a homogeneous response to the increase in suction to –125 mmHg was observed by Morykwas et al. (increase in perfusion and decrease to baseline levels within the first 10 minutes),<sup>24,89</sup> Rejzek et al. found more heterogeneous curve patterns.<sup>91</sup> They observed different responses to identical influences and demonstrated that an increase in suction led to both an increase and a decrease, and also to a constant pattern of perfusion. The question whether these differences, observed using the same measuring method, relate to methodical differences between the two studies (animal experiment in five pigs / human experiment in seven patients; artificial, uncomplicated acute wound after skin excision/venous ulcers subcutaneous measurement/measurement in the wound edge and transcutaneous measurement) cannot be answered. On the whole, a direct increase in flow after application of suction cannot be reliably derived from the diagrams presented by the two groups.

The presumed increase in perfusion would result in an improved oxygenation of the wound edges. However, the research group of Lange et al. was unable to demonstrate any changes in tissue oxygen partial pressure during NPWT with the polarographic measuring technique.<sup>94</sup> Studies by Banwell and Kamolz<sup>54,95</sup> and Schrank et al.<sup>96</sup> also do not demonstrate an NPWT associated increase in flow. These groups found indications that NPWT is advantageous in the early stage therapy of burn wounds (>24 hours after initiation of therapy) for the nutritive perfusion status of the tissue. However, one must bear in mind that NPWT exerts compression on the tissue which in turn usually responds with increased swelling after a trauma or burn injury. So, the improvement of

nutritive perfusion due to NPWT is more likely the result of an indirect anti-oedematous effect that promotes perfusion.

However, a different explanation is also conceivable. In these studies, perfusion was not measured until the compressive NPWT dressing had been removed. As the dressing exerts a more or less strong pressure on the tissue, depending on the intensity of the applied suction, the reported increased perfusion could simply be the result of reactive hyperaemia. The measurement after removal of the dressing is no proof that perfusion is increased when the NPWT dressing is in place. This explanation has also to be taken into account when interpreting the results of Chen et al.<sup>97</sup> They observed increasing capillary calibre and blood volume 'during' NPWT by analysing the wound bed microcirculation by means of microscope and image pattern analysis.

Assessing inguinal and peristernal wounds in recent studies addressing this question, the research group of Wackenfors et al.<sup>93,98</sup> showed that when a suction of -50 to -200 mmHg is applied, depending on the subatmospheric pressure used, hypoperfusion occurs in the subcutaneous and muscle tissue directly adjacent to the wound edge, (1.0–2.6 cm versus 0.5–1.7 cm) while hyperperfusion occurs at a distance of 3.0–3.5 cm (subcutaneous tissue) versus the distance of 1.5–2.5 cm (muscle) and no changes at all in baseline levels at a distance of approximately 3.5 cm (muscle) and 4.5 cm (subcutaneous tissue). Thus, the volume of hypoperfusion increases under the influence of higher pressure values and is dependent on the tissue, for example the hypoperfused area measured from the peristernal wound edge, which expands from 0.5 cm at -50 mmHg to 1.4 cm at -200 mmHg (muscle tissue) and from 1.0 cm at -50 mmHg to 2.6 cm at -200 mmHg (subcutaneous tissue). In muscle tissue, the area of hypoperfused tissue is much

smaller. The explanation for this finding may be that subcutaneous tissue collapses more easily during pressure, which results in a large zone of hypoperfusion proximal to the wound.<sup>98</sup>

Against this background the same group examined the effects of NPWT on peristernal soft tissue blood flow after internal mammary artery harvesting. For this, microvascular blood flow was measured using laser Doppler velocimetry in a porcine sternotomy wound model. The effect of NPWT on blood flow to the wound edge was investigated on the right side, where the internal mammary artery was intact, and on the left side, where the internal mammary artery had been removed. The investigators observed that before removal of the left internal mammary artery, the blood flow was similar in the right and left peristernal wound edges. When the left internal mammary artery was surgically removed, the blood flow on the left side decreased, while the skin blood flow was not affected. Then NPWT (suction pressure -75 mmHg and -125 mmHg) induced an immediate increase in wound edge blood flow similar both on the right side, where the internal mammary artery was intact, and on the left side, where it had been removed. They concluded that NPWT stimulates blood flow in the peristernal thoracic wall after internal mammary artery harvesting.<sup>99</sup> Additionally, the research group from Sweden examined the effect of topical negative pressure on the blood and fluid content in the sternal bone marrow in a porcine sternotomy where the left internal thoracic artery had been harvested followed by NPWT. Magnetic resonance imaging (T2-STIR measurements) showed that NPWT increases tissue fluid and/or blood content in sternotomy wound edges and creates a pressure gradient that presumably draws fluid from the surrounding tissue to the sternal wound edge and into the vacuum source. This 'endogenous drainage' may be one possible mechanism through which the treatment of sternal osteitis is supported by NPWT.<sup>100</sup>

Further evidence for NPWT effects on tissue perfusion in stretched tissues surrounding an open wound were obtained using direct video microscopy.<sup>101</sup> Using alternative surface-probe laser Doppler techniques, others have demonstrated significant increases in relative perfusion in intact skin in healthy volunteers.<sup>92</sup> An abstract of a preliminary study with the O<sub>2</sub>C device (perfusion assessment tool), again on healthy volunteers, also showed some increase in perfusion upon application of a single-use NPWT device.<sup>102</sup> It is possible that the establishment of adjacent hypo and hyperperfused tissue zones may be advantageous in the wound healing process. Increased blood flow may lead to improved oxygen and nutrient supply to the tissue, as well as improved penetration of antibiotics and the removal of waste products.

The mechanism behind the increase in blood flow has not yet been identified, but it has been speculated that the negative pressure causes a force in the tissue that opens up the capillaries, increasing flow. As has been shown both *in vitro* (in processed meat) and *in vivo* (in human wounds),<sup>51,52</sup> blood flow reduction occurs in response to the negative pressure compressing the tissue surface. When tissue perfusion is reduced, angiogenic factors are released to stimulate the formation of new blood vessels.<sup>103</sup> This may promote granulation tissue formation and wound healing. By using another technique to visualise the microcirculation by intravital microscope system in animal experiments Sano et al. demonstrated a significant increase of blood flow at 1 minute after NPWT application, which was sustained for 5 minutes—a result which is influenced by the nitric oxide (NO) synthesis network.<sup>104</sup> In another recent study Hu et al. investigated the effect and mechanism of NPWT combined with open bone grafting to promote bone graft vascularisation. Based on X-ray imaging, fluorescent bone labelling, measurement of calcium content in the callus,

and of expression of fibroblast growth factor-2 (FGF-2) in bone allografts by Western blot analysis they demonstrated that the callus was larger, contained more calcium ( $p < 0.05$ ), and expressed FGF-2 at higher levels ( $p < 0.05$ ) in the NPWT group. Thus NPWT combined with open bone grafting promoted bone graft vascularisation.<sup>105</sup>

Reviewing all studies presented here, it can be postulated that NPWT induces a change in microvascular blood flow that is dependent on the pressure applied, the distance from the wound edge, and the tissue type. It may be beneficial to tailor the level of negative pressure used for NPWT according to the wound tissue composition. A higher pressure level applied during NPWT has a negative effect on the microcirculatory blood flow onto the surface of the wound bed. In soft tissue, particularly in subcutaneous tissue, it is possible for ischaemic states to occur.

### Angiogenesis and the formation of granulation tissue

Granulation tissue is the combination of small vessels and connective tissue that forms in the wound bed. It provides a nutrient-rich matrix that allows epidermal cells to migrate over the bed of the wound. Angiogenesis and evidence for such effects has been described in a diabetic mouse model, in which the highest concentrations of VEGF were detected in the wound edge during treatment of NPWT.<sup>24,26,106,107</sup>

### Change in bacterial count, bacterial clearance and immunological effects

NPWT offers a closed system for wound healing, as the adhesive drape provides a barrier against secondary infection from an external source and has been suggested to reduce the bacterial load in the wound. A reduction of the wound infection rate and the degree of bacterial load has been described as a secondary endpoint in several publications.<sup>31,86</sup> There are only two



studies on this subject, Morykwas et al.<sup>24</sup> and Moues et al.,<sup>108</sup> in which the results of NPWT were investigated in comparison with conventional therapy. In an animal study (5 pigs)<sup>24</sup> the degree of bacterial clearance in acute artificial wounds after inoculation of Gram-positive cocci (two were inoculated with *Staphylococcus aureus* and three with *Staphylococcus epidermidis*) was investigated. Moues et al. analysed the clearance of a total of 50 different bacterial species<sup>108</sup> in human wounds of different ages and origins (n=54). The favourable result might thus be assumed at least for acute, artificially created and infected wounds under optimal healing conditions. However, another paper has found that the bacterial load remains high in NPWT foam, and that routine changing does not reduce the load.<sup>109</sup>

However, the results of Moues et al. appear contradictory. Although they show a reduction in the number of colonies/gram of wound tissue (as determined with the aid of biopsies), the favourable result of the reduction of the bacterial load is limited to Gram-negative bacteria. Contrary to Morykwas et al., the study occasionally demonstrates an increase in Gram-positive staphylococci in the tissue during NPWT. Unfortunately, the two patient groups that were compared in the Moues study are so inhomogeneous in terms of age and origin of the wounds that, strictly speaking, no exact comparison of the two groups is possible from a critical point of view. Two to three-fifths of the patients in both groups of the Moues study were treated with antibiotics, which could result in bacterial selection. Also, there is no information on the possibly different degrees of contamination in the individual wounds at the beginning of the treatment and the proportion of acute and chronic wounds. Nevertheless, this study illustrates that NPWT does not always produce a quantitative reduction of the bacterial load in contaminated human wounds. It is even possible that an increase

in the bacterial count will develop for individual species. This observation is also confirmed in the retrospective study by Weed et al.<sup>110</sup> in which the bacterial load was analysed before, during and after NPWT. Here, there was an overall trend towards an increase in the bacterial count, which increased by 43%, while remaining constant in 35% and decreasing in only 22% of cases. It must be emphasised that the degree of bacterial colonisation was unrelated to the success or failure of NPWT. Wound healing without problems, even in wounds with bacterial contamination, could be observed in all three studies. Wounds with  $>10^6$  bacteria/gram of tissue healed without problems while some wounds did not heal despite a low bacterial load ( $<10^5$  bacteria/gram of tissue). Thus, the question arises whether the bacterial load that remains under NPWT (or other procedures) really must always be considered to be a critical element for wound healing. It also remains doubtful whether more frequent dressing changes would have had a more favourable effect on the degree of bacterial clearance. On the whole, it appears likely that acute, purely superficially contaminated wounds (as in the model of the Morykwas study) can be decontaminated more easily by the application of NPWT than chronic wounds, which are also contaminated in the deeper layers. So, in conclusion it cannot with certainty be established whether NPWT reduces bacterial load in the wound or not. It is exceedingly important to perform proper debridement between dressing changes to mechanically remove the microorganisms. It is well known that the majority of wounds contain bacterial biofilms<sup>111</sup> that are difficult to treat if not debrided frequently, as they can return to their original status within 48–72 hours of the last debridement.<sup>112</sup>

A few other publications provide some insight into the pathophysiology of local and systemic immunological effects of NPWT. An accumulation of activated T-lymphocytes could be demonstrated

in the NPWT foam.<sup>113</sup> This finding could indicate that the foam should not be regarded as immunologically inert under therapy; due to the accumulation of immunologically competent cells, immunologically relevant reactions could take place at the interface between foam and tissue. However, the number of granulocytes in the wound was reduced.<sup>114</sup> According to Buttenschoen,<sup>115</sup> NPWT does not seem to have a major effect on whole-body inflammation. No relevant changes could be demonstrated for the parameter interleukin-6, which is considered a highly sensitive marker for inflammatory whole-body reactions. They could not prove to what degree the endotoxin values are a marker for a potential systemic effect of NPWT. Furthermore, two studies gave no insights into one part of the cytokine network influenced by NPWT.<sup>116, 117</sup>

### Molecular mechanisms in wound healing

The positive effects of NPWT are attributed to the effects of the vacuum-related mechanical stimulus on cell function, protein synthesis and gene expression with resulting matrix-molecule synthesis and cell proliferation.<sup>24,108,118</sup> However, this explanation is given as a mere conclusion by analogy to the results of the scientific investigation of the effects of callus distraction. In fact, there are hardly any studies that investigate the cellular effects of NPWT.

Walgenbach, showed a proliferation activity of endothelial cells in the newly formed granulation tissue after the application of NPWT.<sup>119</sup> When analysing wound exudate samples from patients with neuropathic diabetic foot ulcers, Kopp was able to show that some growth factor concentrations increase, both during NPWT and under the control treatment (hydrocolloid dressing).<sup>120</sup> It should be noted that there are no currently available data suggesting that wounds with a high endogenous cytokine concentration in the wound exudate have more favourable healing. Numerous studies

have shown that the exogenous application of the previously mentioned cytokines has a favourable effect on wound healing.<sup>121–126</sup> It seems possible that NPWT, which produces a comparatively higher VEGF/platelet derived growth factor (PDGF) concentration, creates more favourable wound healing conditions. Note: there is a non-linear interaction in the complex cytokine network.<sup>127–129</sup>

The role of proteases was assessed by Succar in 2014<sup>130</sup> suggesting that mouse mast cell proteases 4, 5, and 6 are mediators of the critical role mast cells play in NPWT in the proliferative phase of healing.

Based on systematic review of the molecular mechanism of action of NPWT, Glass et al. demonstrated that cytokine and growth factor expression profiles under NPWT suggest the promotion of wound healing occurs by modulation of cytokines. This leads to an anti-inflammatory profile and mechanoreceptor and chemoreceptor-mediated cell signalling, culminating in angiogenesis, extracellular matrix remodelling and deposition of granulation tissue.<sup>131</sup>

By assessing the localisation and time-course of the cell division control protein 42 (Cdc42) in cell membrane at ambient pressure it could be shown that NPWT may facilitate cell migration to accelerate wound healing.<sup>132</sup>

When investigating the effect of NPWT on the expression of hypoxia-induced factor 1 $\alpha$  (HIF-1 $\alpha$ ), the authors showed that the expression of HIF-1 $\alpha$  and amount of VEGF were increased by NPWT. This enhances the differentiated state of vascular endothelial cells (VECs) and construction of nucleated blood cells (NBCs), which are advantageous for vascularisation and wound healing.<sup>133</sup>

It is hypothesised that the NPWT device induces the production of pro-angiogenic factors and

promotes the formation of granulation tissue and healing. Jacobs<sup>134</sup> found that wounds treated with NPWT showed significant accelerated wound closure rates, increased pro-angiogenic growth factor production and improved collagen deposition.

First insights into the molecular mechanisms behind NPWT suggest gene expression changes induced by NPWT. Postoperative gene expression changes were compared between NPWT and control patients showing NPWT induced major changes in gene expression during healing. These changes ranged from 10-fold induction to 27-fold suppression. The genes most induced were associated with cell proliferation and inflammation, and the most down-regulated genes were linked to epidermal differentiation. NPWT enhances specific inflammatory gene expression at the acute phase associated with epithelial migration and wound healing.<sup>135</sup> However, its continued use may inhibit epithelial differentiation.<sup>135</sup> NPWT is also associated with an up-regulation of basic fibroblast growth factor (bFGF) and extracellular signal-regulated kinase (ERK) 1/2 signalling, which may be involved in promoting the NPWT-mediated wound healing response.<sup>136</sup>

NPWT influences the local expression of pro inflammatory cytokines in tissue or fluid from acute infected soft-tissue wounds (full-thickness wounds, rabbits). The authors could demonstrate increased local IL-1 $\beta$  and IL-8 expression in early phase of inflammation, which may trigger accumulation of neutrophils and thus accelerate bacterial clearance.<sup>137</sup>

#### Effect on topical antibiotic concentrations

Using a canine experimental model, NPWT treatment of surgically created wounds does not statistically impact cefazolin tissue concentrations when compared with conventional nonadherent bandage therapy as Coutin et al. could show.<sup>138</sup>

Cefazolin wound tissue and plasma concentrations were measured by liquid chromatography mass spectrometry (LC-MS/MS). At the time of surgery and at each subsequent bandage change, wound beds were swabbed and submitted for aerobic and anaerobic culture. After initiating cefazolin treatment, wound tissue antibiotic concentrations between treatment groups were not significantly different at any sampling time. Similarly, after initiating cefazolin treatment, plasma cefazolin concentrations were not significantly different at any sampling time.<sup>138</sup>

## General points

There are a number of different treatment variables. The level of negative pressure, the wound filler material (foam or gauze), the presence of wound contact layers, the pressure application mode (continuous, intermittent, or variable), or instillation of fluid may be chosen according to patient needs, disease, wound type and shape. The healing process may be influenced by varying these parameters. There is widespread clinical experience, but few clinical controlled trials, to support the idea that adjusting the variables of treatment may minimise complications, such as ischemia and pain, and optimise outcome. There follows some of the evidence and thoughts of individualisation of treatment that exists to date. The rationale for each of these modification options is briefly addressed below:

- Pressure level/suction strength
- Vacuum source (storage-battery operated therapy units, wound drainage systems)
- Intermittent or continuous modus
- Wound fillers (polyurethane foam, polyvinyl alcohol foam, gauze)

- Wound contact layers
- NPWT and dermal replacement
- Protection of tissue and organs
- Pain treatment
- NPWT and adjunct therapies
- Other points.

### Pressure level/suction strength

There is an accumulation of evidence suggesting the effective range of negative pressure is between  $-50\text{mmHg}$  and  $-150\text{mmHg}$ .<sup>139</sup> There is however, little information on the optimum level of negative pressure for clinical use and it has been speculated that the level of negative pressure may be adjusted in a number of circumstances. Pressure distribution into the wound depends on the direct contact between the wound filler and the wound tissues. Tissue that is not in contact with the wound filler will not be subject to suction force, as seen in a sternotomy study.<sup>140</sup> A wound contact layer slightly lowers the level of negative pressure that affects the tissue level.<sup>141</sup>

According to findings published from an animal study by Morykwas et al., a suction level of  $-125\text{mmHg}$  was suggested for many years as the optimal suction strength for new tissue formation and wound cleansing. However, it was found that the capacity to vary the suction strength can be useful under certain circumstances. For instance, in certain cases of patients with pain and with poorly perfused deep soft tissue it can be appropriate to choose a suction setting less than  $-125\text{mmHg}$ .<sup>142,143</sup>

Overall, the studies give a reliable indication that there are positive pressure values at the interface between foam and wound surface ('underneath' the foam).<sup>144-146</sup> Interestingly, it has been shown

that the pressure in the tissue is positive and not negative pressure. In a study of free flaps, a range of positive pressures from  $+8\text{mmHg}$  and  $+12\text{mmHg}$  was detected when NPWT was varied from  $-50\text{mmHg}$  to  $-150\text{mmHg}$ .<sup>147</sup> Kairinos et al., in a wound model of processed meat, showed that there is increased pressure 1 cm into the wound edge tissue and also clinically in thin grafts under NPWT.<sup>51,52</sup> In experiments a spectrum of pressure values of  $-6\text{mmHg}$  to  $1-5\text{mmHg}$  (the latter value at a suction strength of  $200\text{mmHg}$ ) were found on the surface of (*ex vivo*) bovine muscle and at a depth of 1–3 mm in the human muscle.<sup>146</sup> Thus, the assumption is that, at least in some parts of the foam/wound-interface, the application of NPWT is associated with positive pressure values. To date, the effects of different suction strengths on wound healing have been analysed in several studies.<sup>148,149</sup> These researchers investigated wound healing and new granulation tissue formation at  $-25$ ,  $-125$  and  $-500\text{mmHg}$ <sup>149</sup> and at  $-25$ ,  $-50$ ,  $-75$  and  $-150\text{mmHg}$ .<sup>148</sup> The two studies concur that a suction of around  $-25\text{mmHg}$  is more unfavourable than a suction strength of around  $-125\text{mmHg}$ . There is only one study with wound healing outcomes of  $-500\text{mmHg}$  and one study for the comparison of the suction values of  $-50$  to  $-150\text{mmHg}$ . No significant difference in the wound area was found between the suction strengths of  $-50$ ,  $-75$  and  $-125\text{mmHg}$ . Unfortunately, none of the research groups analysed the suction range of  $-50$  to  $-200\text{mmHg}$ , which is normally used (commercially available vacuum sources). Pressures as low as  $-40\text{mmHg}$  may be used for the treatment of sensitive, poorly perfused tissue. These levels of negative pressure are shown to provide about half the maximal blood flow effect in a porcine peripheral wound study.<sup>150</sup> According to the same study,<sup>150</sup> levels of negative pressure higher than  $-80\text{mmHg}$  are seldom necessary. However, in another study on porcine peripheral wounds it was suggested that exudate drainage may be improved at  $-125\text{mmHg}$ . This pressure could be used for the first few days to treat high-output wounds, after which

the negative pressure may be lowered as the amount of exudate lessens.<sup>150</sup>

Low pressures may be ineffective, whereas high pressures may be painful and have a negative effect on the microcirculation. Generally, pressures between  $-75$  and  $-125$  mmHg have been suggested. The most commonly used pressure is  $-125$  mmHg, is based on 1997 research.<sup>25</sup> Experimental studies in pigs have shown that the maximal biological effects on the wound edges in terms of wound contraction,<sup>150</sup> regional blood flow<sup>150</sup> and the formation of granulation tissue<sup>151</sup> are obtained at  $-80$  mmHg. A recent case report concurs that negative pressure levels lower than  $-125$  mmHg result in excellent wound healing.<sup>152</sup>

Based on the observation that higher suction values generate hypoperfused areas of a larger volume and that there are no significant differences in wound area reduction between the suction strengths of  $-50$ ,  $-75$  and  $-125$  mmHg, it may be assumed that a reduction of the usually selected suction strength from  $-125$  mmHg to less than  $-100$  mmHg is at least not detrimental and protects poorly perfused tissue. This statement is supported by a porcine study, which hypothesised that instead of the highest negative pressure value, the suitable value for NPWT is the one which is the most effective on regulating wound relative cytokines. Analysing the bacterial count, histological and immunohistochemical examination and Western blot testing of the expression of VEGF and bFGF showed that comparing with vigorous negative pressure, relatively moderate pressures contribute to wound healing via accelerated granulation growth, increased angiogenic factor production and improved collagen fibre deposition.<sup>153</sup>

Special attention with regard the pressure level may be made when there is a risk for ischaemia, for example in the case of circumferential dressings,

vascular disease, diabetic foot ulcers (DFUs) and thin skin transplants, or when patient can experience pain during treatment.<sup>93,139,152,154-160</sup>

In these circumstances, a high level of negative pressure should not be applied because of the risk for ischaemic injury to the tissues.

In summary, between  $-75$  and  $-125$  mmHg has been suggested, but special considerations have to be taken into account when dealing with the treatment of sensitive, poorly perfused tissue and highly exuding wounds.

### Vacuum source

Today several NPWT devices are available. They are battery powered or mechanically driven. All these devices allow the patient to be mobile and independent from hospital's wall-suction on the ward and to be treated by NPWT in the home care setting. Some battery-powered NPWT units use an electronically controlled feedback system that ensures the maintenance of the selected pressure level (for example,  $-50$  to  $-200$  mmHg) even in the presence of small air leaks, guaranteeing the effectiveness of NPWT.

The electronically controlled feedback system, not implemented in all mechanical systems, ensures the maintenance of the selected pressure level giving the patient higher safety. Additionally, mostly audiovisual alarms alert the staff and the patients to large air leaks (loss of seal), blockage of the tubing and full canisters (content between 125 ml and 1000 ml). These therapy units are designed to reduce complication and allow faults to be promptly recognised. If the patient is mobile, smaller vacuum sources should be used, which can easily be worn on a strap over the shoulder or around the neck (particularly suitable for outpatient therapy). Some of the smaller devices are disposable NPWT devices producing a vacuum between  $-80$  and  $-125$  mmHg. Some of these single-use NPWT systems are canisterless and

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manage wound fluid through a combination of absorbing materials and highly breathable film within the dressing.

Traditional NPWT systems use an electrically powered pump to generate negative pressure at the wound bed. Developments since 2010 have led to the introduction of portable devices that deliver NPWT without the use of an electrically powered pump. These smaller light-weight devices are mechanically powered and generate continuous subatmospheric pressure level to the wound bed between  $-75$  and  $-125$  mmHg. In comparison with electrically powered NPWT system, the mechanically powered systems, in smaller wounds, showed similar biomechanical properties, functional wound-healing benefits and a clinically suitable usability for both clinicians and patients.<sup>161-167</sup> This technology has demonstrated similar efficacy and increased usability for both clinicians and patients when compared with electrically powered NPWT devices.

#### Intermittent or continuous modus

The different equipment also allows determining the mode of administration of the pressure that may be applied in a continuous or intermittent mode. Negative pressure is most commonly applied in the continuous mode. Intermittent mode involves repeatedly switching on and off (usually 5 minutes on to 2 minutes off), while variable NPWT provides a smooth cycling between two different levels of negative pressure. There are experimental indications that NPWT with intermittent suction may be of benefit for wound healing. Morykwas et al., for instance, showed that new granulation tissue formation is significantly greater in intermittent suction mode than in continuous suction mode.<sup>24</sup> On the other hand, intermittent therapy may result in a higher occurrence of pain in the treated patients. However, it should be considered that new pressure cycles, without going to 0 mmHg

suction, but only lowering the suction, to 50% for example, should be able to maintain the highest degree of blood vessel formation and also a significant decrease in pain compared with the traditional intermittent group.<sup>168</sup> Thus, using variable NPWT in this mode, the patient discomfort decreased while maintaining superior wound healing effects as the intermittent mode. The therapy applied with intermittent mode produces a mechanical stimulation of the wound bed (a massaging effect)<sup>169</sup> and a greater circulatory stimuli,<sup>170</sup> oxygenation and angiogenesis, and presumably a lower risk of occurrence of ischaemic damage.

It has been suggested that therapy may be applied in continuous mode for the first 24 hours and possibly, if you want the effects above, changed to the intermittent mode (IM).<sup>139</sup> An *in vitro* model of infected wound with no blood flow like necrotic tissue, was used to investigate the effect of various types of negative pressure on the proliferation potency of non-pathogenic *Escherichia coli*. The proliferation potency of *Escherichia coli* was higher under intermittent negative pressure rather than under continuous negative pressure and higher under intermittent negative pressure with a short cycle than with a long cycle.<sup>171</sup> It should be remembered that, in clinical practice, the continuous mode is still the most widely used NPWT option. This is against the background of the literature supporting wound healing using the IM in comparison with the continuous mode. Thus, there is a disparity between science (valid reasons to use the IM) and the current practice (almost no use of IM).<sup>172</sup> Nevertheless, under special wound conditions, when the wound involves structures such as the peritoneum, between toes, in tunnelling injuries, in sternotomies, in the presence of high levels of exudate and when using NPWT on grafts or skin flaps, the continuous mode is the option of choice.

## Wound fillers

For NPWT it is necessary to fill the wound with a compressible open porous material. For this, there are foams and gauze available with different properties such as pore size and stability. Several studies<sup>57</sup> have shown that the choice of wound filler material has considerable influence on the wound healing process. There are also technical considerations during the application of a wound filler for NPWT. PVA foam, for NPWT was the first used material (since 1988, white foam, pore size 60–1500 µm), a slightly firmer and less pliable with low risk of ingrowth. Today, polyurethane foam is the most widely used type of wound filler, introduced 1997, pore size 400–600 µm, soft, black. It forms a fairly strong mechanical bond with the wound tissue after approximately three to four days due to the ingrowth of granulation tissue. The foam should be changed after two to three days. In 2007, gauze was introduced to the market as a filler for use with NPWT.<sup>173</sup> The gauze has a spiral shape and is impregnated with an antiseptic substance (0.2% PHMB). Numerous studies have shown the wound healing effects of gauze.<sup>174–176</sup> It should be noted that pressure distribution is similar for gauze and foam in dry wounds and the differences in performance is rather related to the structure of the material and its mechanical effects in the wound, as shown in a porcine study.<sup>177</sup> In a wet wound using gauze a perforated drainage tube should be inserted into the wound filler to apply a good pressure transduction to the wound bed.<sup>178</sup> The degrees of micro- and macrodeformation<sup>57</sup> of the wound bed are similar after NPWT regardless of whether foam or gauze is used as wound filler.

The biological effects of NPWT depend on the type of wound filler. Blood flow was found to decrease 0.5 cm laterally from the wound edge and increase 2.5 cm from the wound edge, but was unaltered 5.0 cm from the wound edge. The increase in blood flow was similar with all wound fillers. The decrease in blood flow was more pronounced

with foam than with gauze. Similarly, wound contraction was more pronounced with foam than with gauze.<sup>179,180</sup> Wound fluid retention was lower in foam, while more fluid was retained in the wound when using bacteria and fungus-binding mesh.<sup>179</sup> NPWT may be tailored to the individual wound type to optimise the effects and minimise the complications by choosing different wound fillers. The choice of filler may be made with regard to the morphology of the wound, the wound characteristics, the patient feedback, possible infection and scar tissue formation.

## Morphology of the wound

There are different types and shapes of wounds. Wounds may be uniform or have irregular beds with or without the presence of undermining. Foam may fit better into a wound with a uniform shape, while gauze may be easier to apply in wounds that have an irregular shape, or with undermining since it can be better manipulated to the shape of the wounds. Different wound fillers can also be combined.<sup>159</sup> In deep wounds, with or without association with an area that is undermined, both fillers may be applied in order to fill the wound efficiently.<sup>139,181</sup> Over a thin graft or a wound sleeve, the gauze also allows us to cover the entire wound in an appropriate manner. Negative pressure is only transmitted to the tissues that are in immediate contact with the wound filler.<sup>140</sup> In complicated wounds with deep pockets, the wound filler must be carefully positioned, and it may be easier to use gauze because it can be adapted to the shape of the wound.<sup>157</sup> Foam may be advantageous for 'bridging therapy' since the foam compresses to a greater extent than, for example, gauze and thereby contracts the wound and speeds up the closure.<sup>154,160</sup>

## Exuding wounds

In heavily exuding wounds, foam at a higher pressure (–120 mmHg) may be useful, since foam is less dense than gauze and a higher level of negative pressure drains the wound quicker.<sup>182</sup>

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### Wounds at risk of ischaemia

NPWT should be applied with caution in wounds at risk of ischaemia.<sup>93,139,154,155,158–160,181</sup> Apart from lowering the level of negative pressure, the clinician may carefully choose and trim the wound filler. Gauze produces slightly less hypoperfusion effects than foam.<sup>183</sup> Gauze and a large piece of foam produces less wound contraction, presumably resulting in less pain, compared with a small piece of foam.<sup>184</sup> Taken together, in circumstances where there is a risk of ischaemia, a lower pressure (–40 to –80 mmHg) and using gauze may be considered.

### Infected wounds

There are various wound fillers designed for infected wounds: foam with silver, gauze that is impregnated with PHMB, gauze that is impregnated with silver. Instillation techniques allow the irrigation of the wound with antiseptic solutions.<sup>139,185</sup> In these situations hydrophilic foams should be used.

Bacteria and fungus binding mesh is an alternative wound filler in NPWT which produces a significant amount of granulation tissue in the wound bed, more than with gauze and without the problems of ingrowth, as with foam.<sup>179,186</sup>

### Tendency to the formulation of excessive granulation tissue

One of the limits to the use of NPWT is the formation of excessive granulation tissue. This may lead to fibrosis, scar tissue, and contractures, which are undesirable when the cosmetic or functional result is important. Biopsies taken of the scar tissue after treatment with gauze showed a minor tissue thickness and disorganisation and less sclerotic components.<sup>175–176</sup> Thus, areas such as joints, where movement of the skin and the underlying tissue occur, may benefit from the use of gauze.<sup>181</sup> Foam allows rapid growth of granulation tissue and may be a better choice in

wounds where large amounts of granulation tissue is desirable, for example, postsurgical wounds such as sternotomy wounds.

Pain upon NPWT dressing removal has been reported and is believed to be associated with granulation tissue growth into micropores present on the foam.<sup>156,187</sup> Wound tissue damage upon removal of the foam may cause the reported pain. Based on assessing released neuropeptides that cause inflammation and signal pain (calcitonin gene-related peptide, substance P), using gauze may be one way of reducing NPWT dressing change-related pain.<sup>188</sup>

### Wound contact layers

In NPWT wound fillers (foam or gauze) are used to ensure that the negative pressure is applied across the entire wound surface. However, there are reports that foam can cause pain and trauma at dressing change.<sup>156,187</sup> For this reason, when foam is used as a filler, a liner—for example bacteria and fungus binding mesh—can also be applied as a wound contact layer.<sup>189</sup> When the clinician anticipates complications, a non-adherent wound contact layer such as paraffin or silicon may be placed over the wound bed beneath the wound filler.<sup>190,191</sup> A wound contact layer also may be placed over vulnerable structures such as blood vessels or nerves<sup>191</sup> as well as over the wound bed itself because it is believed to protect against ingrowth of granulation tissue into foam.<sup>190</sup>

In the clinical setting, the presence of a wound contact layer may reduce the pain during dressing changes as has been reported in several case studies.<sup>190–193</sup> However, studies in an experimental porcine wound model have shown that a wound bed under a non-adherent wound contact layer is devoid of microdeformation and has less granulation tissue than a wound bed in direct contact with the wound filler.<sup>183</sup> The reason



for the difference in effect between a wound filler and a wound contact layer is that the structure of the material in the dressing in direct contact with the wound bed determines the effects of NPWT on the wound bed.<sup>151,183</sup> Therefore, it is important to use wound contact layers only when there are structures to protect, in order not slow healing.<sup>194</sup>

### NPWT and dermal replacement

The use of synthetic dermal replacements (SDRs) in the treatment of large wounds, which have associated morbidity and mortality, has attracted great interest.<sup>195,196</sup> For this, NPWT systems can be used as a securing adjunct to collagen-elastin dermal templates to the wound bed. NPWT is effective for bolstering single-stage collagen-elastin dermal templates onto wounds.<sup>197</sup> Additionally, positive results were reported in acute and chronic non-healing wounds reconstructed with a commercially available bilayer, acellular dermal replacement (ADR) containing a collagen-glycosaminoglycan dermal template and a silicone outer layer combined with NPWT bolstering followed by split-thickness skin graft.<sup>198-202</sup>

Treating with dermal replacements, NPWT can be used to secure the artificial substitutes and in a second step to support the epithelialisation of the dermal replacements.<sup>203</sup> In well-perfused wounds both steps securing the dermal replacement and bolstering the skin graft can be performed simultaneously by NPWT. Additionally, NPWT generates an increased endothelial cell migration resulting in a stimulation of the angiogenic response.<sup>195</sup> In several cases this combination of SDR/NPWT and skin graft/NPWT could substitute free flap surgery in single catastrophic situations after multiple free flap failure, in major third-degree flame burns or due to the patient's poor general condition.<sup>204,205</sup>

### Protections of tissue and organs

Within the choice of the use of NPWT, the clinician needs to consider the presence of exposed

organs or other sensitive structures in the wound due to the risk for severe complication. In 2003, Abu-Omar et al. described two cases of right ventricular rupture during NPWT of the sternum due to mediastinitis following coronary artery bypass grafting (CABG).<sup>206</sup> In 2006, Sartipy et al. reported five additional cases of right ventricular rupture following NPWT in patients treated for post-CABG mediastinitis, three of which died.<sup>207</sup> The risk of right ventricular rupture and bypass graft bleeding following NPWT of mediastinitis is estimated to be between 4–7% of all cases treated.<sup>206-216</sup> Severe bleeding of large blood vessels such as the aorta has also been reported in several patients receiving NPWT.<sup>212,215</sup> NPWT has shown good results in treating postoperative infections in peripheral vascular grafts,<sup>217</sup> but here too, reports of bleeding have started to emerge. The incidence of NPWT-related bleeding in patients with exposed blood vessels or vascular grafts (such as femoral and femoral-popliteal grafts) in groin wounds were relevant in some studies.<sup>218</sup> Severe bleeding has also been reported in patients receiving NPWT for burn wounds.<sup>219</sup>

Reports of deaths and serious complications associated with NPWT led to two alerts being issued by the FDA, in 2009 and 2011,<sup>220,221</sup> stating that during a four-year period, NPWT had caused 174 injuries and 12 deaths, nine (75%) of which, were related to bleeding, in the US alone. According to the FDA, bleeding of exposed blood vessel grafts during NPWT, due to, for example, graft-related infections continues to be the most serious adverse event. These disturbing reports caused the FDA to state that NPWT is contraindicated<sup>221</sup> in certain types of wounds: those with necrotic tissue with eschar, in non-enteric and unexplored fistulas, where malignancy is present, in wounds with exposed vasculature, anastomotic sites, exposed nerves, exposed organs and untreated osteomyelitis.

Despite this NPWT is the only measure a clinician may have to manage a severe infection such as deep sternal wound infection and off-label use (use outside the manufacturer's recommendations, in which case the patient should be closely monitored by the responsible physician) has continued as there are no alternatives that give comparable results. For example, Petzina et al. showed that mortality due to mediastinitis was reduced from 25% to 6% when using NPWT, compared with conventional treatment, even with the risk of right ventricular rupture.<sup>222</sup> Good results have also been reported during NPWT of infected vascular grafts.<sup>217</sup> As the number of complications arising from NPWT treatment has increased, the importance of protecting exposed organs (for example, blood vessels) has been emphasised in the international scientific literature.<sup>210,223–226</sup>

It has been suggested that exposed sensitive structures need to be protected either through the interposition of autologous tissue (muscle flaps) or with heterologous material (dermal substitutes) or a number of wound contact layers. A number of studies have analysed the possibility of applying protective discs over exposed structures.<sup>227–229</sup> The technique has been proven efficacious in protecting the heart<sup>227–232</sup> and reducing the NPWT effects on large blood vessels.<sup>233–235</sup> It is recommended that patients treated outside the manufacturer's recommendations should always be closely monitored and documented.

### Pain treatment

NPWT is considered an effective wound treatment, but there are a number of issues that need to be addressed for improvements to be made. Several studies reported varying levels of pain in patients undergoing NPWT, with certain treatment factors affecting the level of pain, such as the NPWT system and the dressing/filler used.<sup>236,237</sup> Adherence varies from patient to patient and depends on the underlying

conditions, the type of injury and the degree of pain. The most painful moment of the NPWT may be at the time of dressing change. Foam has micropores that enable the growth of granulation tissue into the dressing,<sup>151,238</sup> as tissue is torn away at the time of dressing change it is more painful.<sup>187,239</sup> However, there is a development in dressings that address this problem.<sup>240</sup>

In patients that are neuropathic or paraplegic, where the pain is not of a significant nature, the filler can be used more efficiently. In patients with low adherence, especially children and the elderly, and on painful lesions (such as pyoderma gangrenosum, burns, PUs and infected wounds), gauze, which not allow ingrowth,<sup>238</sup> tends to be better tolerated. Gauze also facilitates dressing changes and reduces the risk of the wound filler becoming attached to the tissue and remaining in the wound,<sup>151</sup> which is of special importance in wounds with deep pockets that are difficult to inspect. Based on the assessment of released neuropeptides that cause inflammation and signal pain, gauze may be one way of reducing NPWT dressing change-related pain,<sup>188</sup> which seems to be related to the more adhesive nature of the foam—probably because of the ingrowth of the granulation tissue in the micropores present on the foam.<sup>187</sup> It has been shown that foam produces greater wound contraction than gauze.<sup>180,184</sup> Another option to reduce pain due to NPWT is to prepare the patient by infiltration of the wound filler with saline solution or local anaesthetics before dressing change. Administration of topical lidocaine into the wound filler has been shown to decrease pain during dressing changes compared with saline. In the study, patients were randomised to receive either 0.2% lidocaine or 0.9% saline administered through the NPWT tubing into the foam dressing 30 minutes before changing the dressing.<sup>241</sup> Other authors have confirmed these results.<sup>242,243</sup>

### NPWT and adjunct therapies

NPWT can work in combination with instillation

of certain fluids more effectively. This combination of NPWTi generates an additional therapeutic option. NPWTi is described in more detail in the section on page 53. Another modification of the traditional NPWT will be the use on closed incisions, ciNPT, to prevent surgical site infections. ciNPT is described in more detail on page 56.

## Indications in specialties

Open fracture-induced soft tissue wounds and the closure of the dermatofasciotomy wound were the first reported indications for NPWT.<sup>244,245</sup> NPWT is now used in more and more indications in orthopaedic surgery, traumatology, plastic and reconstructive surgery and is a treatment option that is implemented in the daily routine of many trauma and orthopaedic departments in Europe. In the following sections the importance of NPWT will be presented in more detail.

### NPWT in acute traumatology and for the closure of dermatofasciotomy wounds

NPWT is a tool in the treatment of traumatic wounds and high-risk incisions after surgery. During the two decades of the use of NPWT, the indications have expanded, allowing its use in a variety of clinical scenarios:<sup>246,247</sup>

- Contaminated acute wounds (open fractures, penetrating injuries, decollement injuries (Morel-Lavallée syndrome)<sup>248,249</sup> and wounds with tissue defects requiring a step wise procedure followed by a delayed primary closure or plastic surgery
- In cases of heavily contaminated wounds or wounds with big tissue defects, the resection of damaged and potentially infected soft tissue and the closure of the debrided wounds are often not feasible and prolonged wound management must be performed
- Where attention has to be paid to the wound cavity: in order to prevent possible retention of wound secretions, it must be completely filled with foam cut to the cavity's dimensions. A plastic surgeon should be consulted at the time of the second look operation in order to plan an early soft tissue closure
- If required, depending on the body part, an additional immobilisation with an external fixator may be performed. The pins of the fixateur can compromise the vacuum seal. In this situation the wound filler (foam or gauze) should be extended to include the fixator
- In cases of incomplete or complete amputations secondary to trauma in which reimplantation is out of question, a definitive repair of the amputation stump is often not possible because of the local and general situation of the patient. Thus, soft tissue debridement as part of damage control will be necessary
- An amputation stump resulting from a guillotine-like marginal zone amputation remains open and a temporary soft tissue coverage by means of NPWT can be the procedure of choice
- NPWT may be used on dermatofasciotomy wounds, decreasing dressing change frequency and minimising soiling of the patient's bed, bed linen, towels and clothing, even in the case of heavily exuding wounds
- After decompressive dermatofasciotomy for compartment syndrome, low-level continuous suction should be used. Particularly, in case of severe ischaemia, NPWT using a pressure value of  $-50$  to  $-100$  mmHg is adequate. The low-level of negative pressure appears to be sufficient to apply tension to the wound edges and to produce an anti-oedema effect.

In general, NPWT does not replace adequate surgical treatment of soft tissue injuries and should be regarded as a temporary measure before definitive treatment of the defect and for wound conditioning. Besides its useful mechanism of action at the cellular level, the mechanical drainage principle and reduction of dead spaces in the wound defects, are important factors for reduction of bacterial colonisation and for prevention of infection in open wounds. Caution is advised when using the method in acute trauma situations where bleeding might occur due either to the localisation of the wound or to an existing systemic coagulation defect. The literature presents 185 peer-reviewed articles dealing with injured and traumatised patients. To date, reports in this surgical literature consist mainly of case reports, nevertheless in the special field of trauma wounds there exist two RCTs.<sup>250,251</sup> The most important conclusions in the literature between 2011 and 2015 are:

- NPWT is a useful treatment option for open fractures, to bridge between initial debridement and final microsurgical tissue transfer. NPWT significantly reduced morbidity and healing time of injuries when compared with previously performed dressing treatments.<sup>252,253</sup> Considering patient comfort, the costs related to the NPWT, and the final flap results, a 7-day interval between changes of the NPWT is acceptable.<sup>252</sup> Other authors observed no disadvantage if patients underwent NPWT for an average of 12 days (range: 1–35) and concluded that traumatic lower limb reconstruction in the delayed period is no longer associated with high rates of flap failure. Improvements in microsurgery and the advent of NPWT have made timing no longer crucial in free flap coverage of traumatic lower limb injuries<sup>254</sup>
- Sequential therapy of NPWT and pedicled flap

transplantation can be regarded as a reliable option to obtain a good outcomes of wound healing and satisfactory functional recovery for the management of motorcycle spoke heel injury<sup>255</sup>

- In clinical situations of traumatised less perfused soft tissue, the suction level for NPWT should be minimised to –50-75-100 mmHg to prevent a further impairment of the perfusion of the soft tissue.<sup>256</sup>
- For perineal trauma-related wounds the use of NPWT led to improvement of local wound conditions faster than traditional dressings, without significant complications, proving to be the best alternative as an adjunct for the treatment, always followed by surgical reconstruction with grafts and flaps<sup>250,257</sup>
- Beside the use of ultrasound and computed tomography in the preoperative evaluation of the penetrating trauma patient, the use of temporary vascular shunts, the use of preperitoneal packing in pelvic fractures and modern rehabilitation-management of the multiple traumatic amputation patient, NPWT is one of the most important innovations in operative trauma surgery since 2000.<sup>258</sup>

The two RCTs (see table, appendix 3) evaluating the impact of NPWT after severe open fractures on deep infection demonstrate that the relative risk ratio for infection in the NPWT group is 0.199 [95% confidence interval(CI): 0.045–0.874], suggesting that patients treated with NPWT were only one-fifth as likely to have an infection compared with patients randomised to the control group. NPWT represents a promising new therapy for severe open fractures after high-energy trauma.<sup>251</sup> Additionally, one group analysing widely applied methods of delayed primary closure of leg fasciotomy (NPWT, shoelace

technique), showed that both NPWT and the shoelace technique are safe, reliable and effective methods for closure of leg fasciotomy wounds. NPWT requires longer time to definite wound closure and is far more expensive than the shoelace technique, especially when additional skin grafting is required.<sup>250</sup>

### Periprosthetic infections of the hip and knee joint

NPWT is a useful option in the management of early or delayed infections following implantation of an endoprosthesis (rate approximately 1–2%). To date, only a few peer-reviewed articles have addressed this subject, two case series (evidence level 4) and two case reports (evidence level 5). The advantages of NPWT for this indication are:

- Large, open wounds can be converted to hygienic, closed wounds
- Wound secretion is continuously collected in a canister
- Contamination from the environment is prevented because the wound is sealed.

The patient benefits from the fact that, even in the case of a heavily draining wound, the dressing requires changing only every 2 to 3 days minimising soiling of the patient's bed and clothing. This increases patients' comfort, while reducing nursing demands. Although the current literature does not provide clinicians with many reports, it seems that the effects of NPWT may contribute to maintaining the implant *in situ*, avoiding the exchange of the prosthesis. A systematic review demonstrated that the algorithm: debridement – lavage – change of modular prosthesis components and NPWT leads to the highest infection eradication rate (92.8%).<sup>259</sup>

NPWTi may further facilitate the treatment

of infected endoprostheses (see pages 53–56). Periprosthetic infection treated by NPWTi with antiseptic solution using a reticulated sponge in combination with NPWT was suggested to be easy and effective to use. With this system, early treatment of periprosthetic infection with antiseptic irrigation in combination with NPWT decreasing the bacterial burden, salvage of prosthesis seems to be possible. Nevertheless, final conclusions about this therapy can only be drawn after examining a larger series of patients.<sup>260</sup> In terms of legal issues and patient safety, treatment outside the manufacturer's recommendations should always be closely monitored and documented.

### NPWT in the treatment of osteomyelitis and surgical site infection

Wound infections even today occur in up to 50% of patients undergoing surgery for traumatic wounds dependent on the grade of soft tissue injury, amount of contamination and other patient and operation-related factors. Treating these postoperative wound infections with NPWT decreases oedema and dead space, theoretically reducing the risk of infection. It also prevents premature walling off of deeper cavities, which can occur with the use of NPWT on superficial defects. NPWT allows for the reduction of the deep cavity defects without delaying wound closure or creating more tissue damage.<sup>261</sup> A systematic review showed that there is an increasing body of data supporting NPWT as an adjunctive modality at all stages of treatment for higher-graded open tibia fractures. There is an association between decreased infection rates and NPWT compared with standard gauze dressings. Additionally, there is an evidence to support NPWT beyond 72 hours without increased infection rates and to support a reduction in flap rates. So, after extended NPWT fewer patients required flaps than grading at the first debridement would have predicted.<sup>262</sup> Besides these topical advantages in the care of infected wounds, NPWT provides a more rapid and comfortable treatment

opportunity, representing a reliable alternative to conventional wound care methods.<sup>263</sup> Even in postoperative joint infections, study results confirm the value of the NPWT following surgical debridement, in combination with resistance-tested antibiotic treatment, as a sufficient therapy for these infections. This procedure leads to safe treatment of the joint infection, combined with good function of the treated joint, good patient comfort and a short duration of the therapy.<sup>264</sup>

In the treatment of osteomyelitis too, the advantage of NPWT is that wound secretion, usually contaminated by bacteria, is constantly drained from the wound by negative pressure. At the same time extravascular fluid is reduced. The basic step in the treatment of osteomyelitis is the radical surgical debridement and necrectomy of infected tissue. Usually, sequential surgeries are necessary to achieve quiescence of the infection. Within this treatment protocol, NPWT as a part of the reconstruction algorithm is used between two revisions as a temporary wound dressing. A promising modification of the technique is NPWTi, in which antiseptic or antibiotic solutions are used to instill the surgical site via the drains and foams (see pages 53–56).

NPWT serves more and more to prevent these infections, by early use to temporarily close trauma wounds after the first debridements and by using ciNPT (see pages 56–59).<sup>265–269</sup> An evidence-based medicine review of military and civilian extremity trauma data provide recommendations for the varying management strategies to care for combat-related extremity injuries to decrease infection rates and showed that postinjury antimicrobial therapy, debridement and irrigation and NPWT are important aspects.<sup>266</sup>

### Exposed tendon, bone and hardware

Exposed tendon, bone and hardware represent a major therapeutic challenge in the surgical

treatment of wounds of the extremities. The coverage of these wounds with split-thickness skin grafts is associated with poor functional results and therefore not recommended in the majority of cases. Wound closure and acceptable functional results can usually be achieved with plastic and reconstructive surgical procedures. Nevertheless, there are situations in which the problem of exposed structures cannot be managed using plastic reconstructive surgery. These include impaired blood flow in the extremity, marked lymphoedema, extension of the injury to adjacent soft tissue or donor sites (especially in extensive burns) and the risk of contamination. In addition, donor site complications can also result in tendon exposure. Soft tissue defects of the limb with exposure of tendons and bones in critically ill patients usually lead to extremity amputation. The temporary coverage of these types of defects was an early application of NPWT. When NPWT was still in its infancy the application of NPWT was found to encourage the formation of granulation tissue over bradytrophic tissue and even over exposed metalwork more rapidly than any other dressing technique. Case series have shown that infection control and limb salvage were achieved in all cases with multiple debridements, topical negative pressure therapy, and skin grafts. In all patients, the exposure of tendons and bones was reversible by this strategy without a free flap transfer. The following conclusions can be made:

- NPWT is the treatment of choice when plastic surgery procedures cannot be used for the coverage of exposed bone, tendon or metalwork. Experimental evidence suggests that intermittent suction at a pressure level of –50 to –125 mmHg should be used for this indication<sup>270</sup>
- NPWT should be considered as a last attempt to prevent amputation in a situation where plastic surgery procedures cannot be used for the coverage of exposed bone, tendon or metalwork<sup>271</sup>

- Even bigger soft tissue defects, for example, with tendon exposure (Achilles tendon) there was complete healing with secondary wound healing (or secondary skin grafting). NPWT is an optional treatment for the complicated wounds where reconstructive surgery with a skin flap cannot be performed.<sup>272</sup>

## NPWT in the treatment of acute burns and scalds

Since 1999 NPWT has been applied in the treatment of burns and scalds.<sup>273,274</sup> After collecting initial positive experiences some research centres compared NPWT with silver sulfadiazine treatment (SSD) in burns, showing that early application of NPWT can improve the quality of healing.<sup>275</sup> To date, there are 66 peer-reviewed articles, including some based on animal experiments, examining with NPWT in burn injured patients. Clinical results of these reports showed that NPWT in the treatment of burn injuries has strong anti-oedematous effects, optimises wound healing, reduces the need for secondary surgery and facilitates care.<sup>54,276</sup> In contrast to those treated with NPWT, conventionally treated patients showed a significant decrease in perfusion as measured by dynamic IC-View laser-fluorescence videography. This positive effect is NPWT-related, due to a pressure-induced reduction or prophylaxis of the connective tissue oedema and resulting in better wound oxygenation and quicker wound healing with less complications in the majority of cases.<sup>96</sup> So, one intraindividually designed study showed that in NPWT treated hands, even with large deep burn injuries, the clinical results were better in comparison with the conventional treatment to the contralateral hand.<sup>54</sup> An investigation in animals indicates that NPWT inhibits the invasion and proliferation of *Pseudomonas aeruginosa* in burn-wounded tissue and decreases early mortality in a murine model

of burn-wound sepsis. These therapeutic benefits likely result from the ability of NPWT to decrease bacterial proliferation on the wound surface, reduce cytokine serum concentrations, and prevent damage to internal organs.<sup>277</sup>

In patients with hand burn injuries it is necessary to consider that NPWT exerts a positive pressure of 6–15 mmHg on the tissue. The pressure intensity is directly dependent on the selection of suction between –50 mmHg and –200 mmHg. This pressure is the reason for the direct anti-oedematous effect of NPWT, which indirectly results in enhanced tissue perfusion. A favourable side effect of this external pressure obviates the need for constant elevation of the patient's hand. Because the foam is stiff under the suction, splint fixation is not necessarily required. Despite the positive effects of NPWT applied at –125 mmHg it should be noted that the induced positive pressures may cause tissue ischaemia in a few cases. Thus, the pressure should be chosen carefully in order that, on the one hand, the anti-oedematous effect can be established but, on the other, that nutritive perfusion is not reduced, even in critically perfused tissue.

Human studies show that therapy should begin within six hours if possible and should be applied continuously for at least 48 hours to reduce the formation of oedema and thus reduce post-burn damages.<sup>54,95,278,279</sup> Based on the experience with superficial and deep dermal hand burns and scalds, NPWT is considered cost-effective, since it reduces treatment time and the requirements on personnel involved in the process, and favourably influences the clinical process.<sup>280</sup>

Other author groups demonstrated a benefit of using the NPWT system in thermal injuries to secure the fixation of skin substitutes, such as tissue-engineered skin substitute and split-skin grafts. NPWT is a highly reliable and reproducible

method to bolster these skin substitutes.<sup>204,205,281,282</sup> Its ability to conform to contours of the body and cover large surface areas makes it especially useful in securing a graft. NPWT as a method of bolstering results in decreased repeat grafting and minimal graft loss, thus decreasing morbidity compared with conventional bolster dressings. The reported overall skin graft take rate was over 95% using suction levels between -75 and -120 mmHg.<sup>283</sup> Negative pressure dressing improves not only graft take in burns patients but can also be considered when wound bed and grafting conditions seem less-than-ideal.<sup>284</sup> A multicentre RCT in burn injury showed, based on extensive wound and scar measurements, highest elasticity in scars treated with the substitute and NPWT, which was significantly better compared with scars treated with the substitute alone.<sup>285</sup>

Even in the treatment of paediatric patients NPWT seems to be successful for fixation of skin substitutes and split-skin graft (continuous mode and -125 mmHg). The main advantage of the technique is a higher mobility of these patients compared with conventional fixation methods. The high compliance rate of an often challenging group of patients such as children recompenses possible higher initial material costs compared with conventional fixation methods.<sup>286,287</sup>

It is possible that the effect that compresses the tissue can also be successfully used for burns on the torso, if appropriate dressings and dressing techniques can be adapted. An enhancement to a technique previously described through the use of long thin strips of NPWT fillers to transmit negative pressure, the enhanced total body wrap, aims to provide ideal conditions to promote healing in burns. Using NPWT, this technique is simple and straightforward enough to be applied in the majority of tertiary centres around the world<sup>288</sup> and in extensive burns (total body wrap concept).<sup>289,290</sup> The management of burns with

their associated high-fluid exudate following burn excision and skin grafting has always posed a challenge in burn wound care. The ideal dressing should protect the wound from physical damage and microorganisms; be comfortable and durable; allow high humidity at the wound; and be able to allow maximal activity for wound healing without retarding or inhibiting any stage of the process. NPWT fulfils all these criteria. Advantages conferred include accurate charting of wound exudate; reduced frequency of dressing changes; lower infection rates through prevention of strike-through; and securing and improving the viability of skin grafts. These advantages can be used on challenging locations such as the open abdomen in severely injured burn patients and skull burns.<sup>291,292</sup>

## Plastic and reconstructive surgery

The field of plastic and reconstructive surgery was the first in which the introduction of NPWT provoked a recognisable change of different therapeutic concepts. NPWT produced a change of paradigms within the treatment algorithms.<sup>293</sup> Therefore, the older improved construct of the traditional reconstructive ladder is updated to reflect the use of NPWT (beside the new developments of dermal matrices).<sup>294,295</sup>

Acute traumas of the lower limbs cause complex functional damage for the association of skin loss with exposed tendons, bones, and/or vessels, extensive soft tissue and osseous destruction as well as heavy contamination requiring a multidisciplinary approach. Once bone fixation and vascular repair have been carried out, the surgical treatment for skin damage is usually based on early coverage with conventional or microsurgical flaps. In these situations NPWT may represent a valid alternative to immediate reconstruction in selected cases of acute complex



traumas of the lower limb.<sup>154</sup> Primary soft tissue reconstruction in complex leg injuries is mandatory in order to protect exposed tissues; however, it may be precluded by the patient's clinical status or by local wound conditions (patients' critical condition for example poly-traumatised patient to prevent the 'second hit', advanced age, medical comorbidities, heavily exuding wounds and questionable viability of soft tissues, need for several debridements).<sup>296–298</sup> In these situations NPWT allows a delay of an early complex reconstructive wound closure by free or local flaps. This is important particularly if there is no availability of plastic surgery due to organisational reasons (for example, war casualties or in a remote area). NPWT improves the wound bed preparation<sup>296,299</sup> for patients with large defects and the temporary coverage during the delay period of 7–15 days (9.7±3.1) when performing the two-step surgical approach to a delayed reverse sural flap for staged reconstruction. The aim is to use the distally based neurofasciocutaneous sural flap to increase the reliability of large sural neurofasciocutaneous flaps.<sup>300</sup>

Similar to burn injured patients, NPWT is a valid tool for reliable fixation of skin substitutes, such as tissue-engineered skin substitute and split-skin grafts in all severe traumatised wounds and is associated with improved graft survival as measured by a reduction in the number of repeated grafts and graft failure complications in adults<sup>204,301</sup> and in children.<sup>302</sup> Thus, in large wounds resulting from severe injuries NPWT significantly increases the tissue-engineered skin substitute take rate to 98±2% in the fibrin/NPWT group (p<0.003) compared with the standard fixation and decrease the mean period from Integra coverage to skin transplantation to only 10±1 days (p<0.002). Therefore, it is suggested that a tissue-engineered skin substitute be used in combination with fibrin glue and NPWT to improve clinical outcomes, shorten hospital stays, with decreased risks of accompanying complications.<sup>303</sup> In a single case

the multilayer-use of two layers of acellular dermal substitutes (interval of approximately one week) combined with NPWT and finally skin grafting combined with NPWT again covered a wider area of exposed tibial bone in a patient who was not a candidate for further free flap surgery after two failed microsurgical plastic procedures.<sup>204</sup> Although NPWT was claimed to be an attractive option for wound care, in one RCT NPWT did not appear to offer a significant improvement over a standard bolster dressing in healing of the donor site (radial forearm free flap) by skin grafting.<sup>304</sup> The majority of RCTs showed an increase of final skin graft take rate,<sup>305,284,305–307</sup> for example, Petkar et al. showed an average graft take of 87.5% (range: 70–100%, SD: 8.73) to an average of 96.7% (range: 90–100%, SD: 3.55; p<0.001). Additionally, review of all RCTs analysing the scar quality showed significantly higher quality after NPWT fixation of skin grafts or other skin substitutes (elasticity, epithelialisation, two-point discrimination).<sup>285,305,307</sup> NPWT appears as a safe and effective adjunct to delayed soft tissue reconstruction in high-risk patients with severe lower extremity injuries, minimising reconstructive requirements and therefore postoperative morbidity.<sup>298</sup>

## Abdominal surgery

The management of open abdomen in severely injured patients or those with serious intra-abdominal infections represents a significant challenge to the surgeon and may include treatment of abdominal compartment syndrome (ACS), effects on respiration, cardiovascular and renal function, and even 'damage control' laparotomy.<sup>308–310</sup> The life-sustaining emergency operations in patients with severe abdominal injuries are often accompanied by visceral oedema, retroperitoneal haematoma or packing of the abdominal cavity. The same applies to re-laparotomies carried out to assess intestinal viability or to control secondary bleeding after damage-control laparotomies, or in

connection with intra-abdominal infections.<sup>311–313</sup> The pressure of forced abdominal wall closure or an abdominal infection may lead to ischaemia and necrosis of the abdominal fascia. The latter results in abdominal rupture with subsequent development of an abdominal wall hernia.<sup>314</sup>

Laparotomies within the scope of ‘damage control’ with packing, the occurrence of ACS or severe septic intra-abdominal complications require repeated revisions of the abdominal cavity. All these situations result in an open abdomen which does not permit primary closure of the fascia and requires temporary abdominal closure (TAC). TAC should prevent contamination of the abdominal cavity, desiccation of intestine and protect the abdominal organs from evisceration and mechanical injury. Currently used TAC techniques include:<sup>311,315–318</sup>

- NPWT
- NPWT in combination with an abdominal re-approximation anchor system (ABRA) or other dynamic suture systems
- Wittmann patch
- Bogota bag (a sterile three litre urine bag positioned on the viscera covered with damp abdominal pad and drape)
- Absorbable or non-absorbable mesh
- Net + zipper.

NPWT has become increasingly established as an additional therapy option in the management of open abdomen. It meets all requirements for TAC with a very low complication rate. NPWT of the open abdomen is carried out using a system specially designed for this indication—abdominal dressing system. A review of the literature reveals 122 peer-reviewed articles (2001–2015, over

n=2307 patients treated in the literature of the last 5 years), mostly case series or case reports, reviews as well some experimental animal studies, assessing the microcirculation of bowel wall during NPWT. The great majority of all articles are of evidence-level 4 or 5 according to the Oxford classification. Only three paper include a randomised comparison with conventional techniques (evidence level 2b).

A recent review underlines the role of NPWT today. For this study, electronic databases were searched to find studies describing the open abdomen in patients of whom 50% or more had peritonitis of a non-traumatic origin. The literature search identified 74 studies describing 78 patient series, comprising 4,358 patients of which 3,461 (79%) had peritonitis. The overall quality of the included studies was low and the indications for open abdominal management differed considerably. NPWT was the most frequently described TAC technique (38 of 78 studies). The highest weighted fascial closure rate was found in a reports describing NPWT with continuous mesh or suture mediated fascial traction (6 studies, 463 patients. Furthermore, the best results in terms of risk of enteroatmospheric fistula were shown for NPWT with continuous fascial traction. Nevertheless, the overall quality of the available evidence was poor, and uniform high evidence-based recommendations cannot be made.<sup>319</sup>

Only three randomised studies were found and considered for review. The main information in these studies was:

- NPWT methods allow the possibility of draining and accounting for fluids collecting in the peritoneal cavity<sup>320</sup>
- NPWT may offer a solution to fascial closure problems and helps prevent peritoneal contamination<sup>320</sup>

- It is suggested that NPWT has advantages when compared with the Bogota bag as a temporary closure method in the management of abdominal compartment syndrome. Decrease in incision width after ACS laparotomy was significantly faster in the NPWT group than in the Bogota bag group (fascia closure was considered appropriate in 16.9 days compared with 20.5 days, respectively)<sup>321</sup>
- Intra-abdominal hypertension prevention is one factor undoubtedly favouring NPWT methods against non-NPWT ones for open abdomen (OA) management in septic peritonitis<sup>320</sup>
- Primary closure rates between groups (NPWT alone (control) or a study group using NPWT plus NPWT-ABRA) were not statistically different, where as the number of trips to the operating room and operating room time use were different. Despite higher Acute Physiology and Chronic Health Evaluation II scores, larger starting wound size, and higher rates of ACS, closure rates in the NPWT-ABRA group were similar to NPWT alone.<sup>318</sup>

In the sum of all published experiences NPWT as a TAC option has gained in importance over the last ten years.<sup>5,322–344</sup> A recent technique of abdominal NPWT differs from the customary NPWT of wounds because of the application of perforated thin polyethylene film positioned between the viscera and the anterior peritoneal wall. A strategy is to use perforated film equipped with a fixed thin foam in the middle, which, under the negative pressure, adheres to the superposed foam layers, preventing any shift of the film in the abdomen. Perforations in the film allow wound secretion flow along the pressure gradient from the abdominal cavity into the receiving vessel of the NPWT device. The foam in lenticular form is positioned over the above mentioned film in two layers and the system is sealed with an adhesive drape. A hole is cut in the centre and a

self-adhesive connecting pad is positioned over it. The latter is connected with the container and the NPWT device. The vacuum source is normally adjusted to  $-100$  to  $-150$  mmHg,<sup>323,324,345</sup> but may go up to  $-175$  mmHg,<sup>341,346</sup> and started. Other authors found a negative pressure of  $-75$  mmHg satisfactory for continual removal of wound fluid and sufficient for approximating the wound edges. This technique prevents adherence of the viscera to the peritoneum and allows the abdominal wall to glide over the bowel loops. At the same time, TAC removal at repeated laparotomies is simple because no adhesions form.

A nationwide prospective observational study of 578 patients treated with an open abdomen (70% abdominal sepsis) in 105 hospitals in the UK (2010–2011, 18 months) support the generally announced importance of abdominal NPWT. In this study the majority of patients (61.4%) were treated with NPWT. Intestinal fistulation [relative risk (RR)=0.83, 95%CI: 0.44–1.58], death [RR: 0.87, 95% CI: 0.64–1.20], bleeding [RR: 0.74, 95% CI: 0.45–1.23], and intestinal failure [RR: 1.00, 95% CI: 0.64–1.57] were no more common in patients receiving NPWT.<sup>347</sup>

The following clinical and experimental experiences with NPWT were published:

### Enterocutaneous fistula

No study revealed any correlation between the occurrences of fistulas before, during, and after NPWT, with diverticulitis being the only risk factor.<sup>348</sup> The rate of enterocutaneous (ECF) development was between 3.5% and almost 20%.<sup>349–352</sup>

### Direct fascial closure

Fascial closure is an additional and particular challenge in patients with an open abdomen. NPWT provides constant medial pressure on the fascial edges and this prevents them from thinning out or retracting over time. This also

facilitates mobilisation of the fasciae and promotes subsequent definitive abdominal wall closure. The negative pressure reported in the literature is non-uniform at  $-75$  up to  $-150$  mmHg. All reports recommend use of continuous suction mode.

Direct or primary fascial closure is possible in 30–89%.<sup>349,353,354</sup> Type and severity of the various early and late consequences in the treatment of an open abdomen are substantially determined by the complication-inducing causes and the basic disease as well as by the options of an efficient in some cases, temporary closure of the abdominal wall. Procedures with highest fascial closure rate have lowest mortality.<sup>355</sup>

Regardless of the underlying pathology (patients with peritonitis, trauma, ACS or abdominal wall dehiscence), high fascial closure rates of 89% can be achieved using a combination of NPWT and mesh-mediated fascial traction (mesh placement at the fascial level).<sup>317,356</sup>

The use of the additional narrowing technique to apply NPWT may explain the high closure rates observed in the patient population of this study. Thus, using a NPWT system, secondary closure of the fascia was obtained in 92%.<sup>350,357</sup> An ABRA combined with the NPWT dressing could be used separately or in conjunction with each other for closure of delayed open abdomen successfully.<sup>358,359</sup> Generally, patients with septic complications achieved a lower rate of fascial closure than non-septic patients but NPWT with dynamic closure remained the best option to achieve fascial closure.<sup>317</sup> The direct comparison with the Bogota bag therapy showed that the number of operations required in the Bogota bag group was significant higher than in the NPWT group (mortality and complication rate significantly lower). The mean time for fascial closure was significantly (three times) longer in the Bogota bag group, compared with NPWT.<sup>360</sup>

### Hernia development

The indication for open abdomen contributed to

the probability of delayed primary fascial closure. NPWT and mesh-mediated fascial traction resulted in a higher fascial closure rate and lower planned hernia rate than methods that did not provide fascial traction.<sup>352</sup>

### Length of hospital and intensive care unit stay

Comparing NPWT results with the control group (mesh-foil laparostomy without negative pressure) resulted in a significant shorter intensive care unit (ICU) and hospital stay.<sup>351</sup>

### Mortality

The number of deaths during hospitalisation in the group treated with NPWT was lower than in the group treated with standard methods.<sup>361</sup> Procedures with the highest fascial closure rate have lowest mortality.<sup>355</sup> The mortality of patients with an enterocutaneous fistula was 17–30%. Generally, in NPWT groups, a significant decrease in mortality was seen, with no statistically significant findings in stratification with c-reactive protein (CRP) and body mass index (BMI). Intraabdominal NPWT offers patients lower morbidity and mortality.<sup>362</sup>

### Other aspects

- It has been suggested, although outside the manufacturers recommendations, that it is possible to use the foam dressing intraperitoneally without a fenestrated polyurethane layer without an increased rate of fistulas.<sup>349</sup>
- NPWT is a reliable tool for infants and children with an open abdomen<sup>363</sup>
- NPWTi is suitable for treatment of an infected open abdomen following pancreatic surgery. NPWTi in one case report had encouraging results and seems suitable to be used as an adjunctive treatment in the management of the infected open abdomen when traditional therapy fails to control the infection<sup>364</sup>

- In animal experiments using laser Doppler velocimetry the microvascular blood flow in the intestinal wall was assessed in pigs where the open abdomen was treated by a temporary abdominal closure dressing and the traditional NPWT dressing. Intestinal wall blood flow significantly reduced to  $64.6 \pm 6.7\%$  ( $p < 0.05$ ) after the application of  $-50$  mmHg using the NPWT dressing, and to  $65.3 \pm 9.6\%$  ( $p < 0.05$ ) after the application of  $-50$  mmHg using a temporary abdominal closure dressing. The blood flow was significantly reduced to  $39.6 \pm 6.7\%$  ( $p < 0.05$ ) after the application of  $-125$  mmHg using NPWT and to  $40.5 \pm 6.2\%$  ( $p < 0.05$ ) after the application of  $-125$  mmHg using the temporary abdominal closure dressing. No significant difference in reduction in blood flow could be observed between the two groups.<sup>365</sup>

To summarise, the use of NPWT in patients requiring open abdomen treatment is reasonable due to the positive results with respect to survival rates and the decrease in the number of gastrointestinal fistulae. A significant faster and higher rate of closure of the abdominal wall was seen. NPWT requires less number of operations, and is associated with a lower complication rate. Thus, NPWT offers patients lower morbidity and mortality and should be defined as a treatment of choice in patients with open abdomen.

## Cardiovascular surgery

The infection of the sternotomy is one of the most feared complications of open cardiothoracic surgery and has a reported incidence that varies between 1% and 5%.<sup>23,35,86,87,366</sup> Preoperative risk factors include age, obesity and diabetes, and intra-operative techniques, such as the use of internal thoracic arteries for the grafts.<sup>367-369</sup> There is a distinction between superficial and deep sternal wound infections (DSWIs). Superficial sternal infections include the skin and subcutaneous

surgical wound, while the deep sternal infections (or post-sternotomy mediastinitis) require at least one of the following criteria: a microorganism isolated from the culture fluid or tissue mediastinum; evidence of mediastinitis during surgically exploration; or chest pain, sternal instability, or fever  $>38^{\circ}\text{C}$ , in combination with purulent drainage from the mediastinum or isolation of a microorganism.

Conventional therapy of these infections was debridement of the wound, open drainage, dressings, broad-spectrum antibiotics, and later reconstructions with the use of flaps, with a strip of greater omentum or muscle flaps and myocutaneous (unilateral and bilateral pectoralis major, rectus abdominis, latissimus dorsi). The mortality rate of patients with mediastinitis is more than 34% higher<sup>23,35,113,131,366,370</sup> than that of patients after cardiac surgery without DSWI (mortality rate 1–5%). Furthermore, postoperative mediastinitis is associated with high morbidity,<sup>371,372</sup> decreased long-term survival,<sup>373, 374</sup> prolonged length of hospital stay<sup>375</sup> and increased costs of care.<sup>376</sup>

In recent years, a less invasive approach has developed using NPWT. As a result of the excellent clinical outcome, NPWT is nowadays the method of choice for poststernotomy mediastinitis.<sup>86,223,377</sup> The use of NPWT has reduced mortality to around 5%, reducing the number and the complexity of treatments and re-operations.<sup>132,378</sup> It shall be noted that sternum is not an indication for NPWT due to underlying exposed structures that may rupture and bleed. The treatment is off-label use and is performed on the clinician's responsibility.

NPWT on closed cardiothoracic incisions is a novel entity with promising results.<sup>379</sup> NPWT over closed incisions to reduce the incidence of deep sternal wound infection was first proposed by Atkins et al.<sup>380</sup> who also investigated perfusion in order to examine potential mechanisms.<sup>381</sup>

Traditional devices were used in which thin strips of silver-impregnated polyurethane foam were applied at –125 mmHg, and in 57 high-risk cases there were no incidence of infection.<sup>380</sup> In a different study, a small case series of ten high-risk patients was reported using a single-use NPWT device, again with no incidences of infection.<sup>382</sup> In a recent randomised clinical study of standard care versus NPWT on closed cardiothoracic incisions was examined in 150 high-risk patients (high age, high BMI and diabetes), the overall rate of sternal wound infection was reduced significantly, from 16% to 4% after five to six days of prophylactic NPWT.<sup>383</sup>

## Vascular surgery

### NPWT of infected blood vessels and vascular grafts

Infections affecting vessels and vascular grafts are feared complications and pose an enormous challenge in vascular surgery. Infections can be limb and life-threatening due to uncontrollable arterial bleeding. The incidence of deep wound infections is approximately 0.6–8%, affecting the groin in two-thirds of the cases. Overall mortality ranges from 10–30%, with 30–70% seen in connection with infected aortic grafts. Infection-related amputations are required in 20–40%. Infections can cause bleeding, systemic sepsis, septic peripheral emboli as well as ischaemia of an extremity, or threaten the life of the patient. The classical management of an infected infra-inguinal graft consists of explantation of the graft and autologous reconstruction or, if not feasible, revascularisation by tunnelling an extra-anatomic graft through non-infected tissue followed by local debridement and wound drainage. In case in which the vessels can be salvaged, the wound is lightly packed with moist gauze for local control. Usually the graft and defect must be covered with a muscular flap.<sup>385–387</sup>

Previously, exposed vessels, grafts or patches are considered to be contraindications and outside

manufacturers recommendations for using NPWT. However, more and more NPWT has been reported to be useful in the treatment of deep perivascular groin infections (Szilagyi grade II and III, exposed vessel or graft). Evidence for the benefit of NPWT in the management of other infected wounds has been amply documented since the 1990's.<sup>24,89,388–394</sup> To date, the results of 263 patients have been reported in 19 articles (evidence level 2a–5), including one systematic review.

There are two studies available characterised by higher evidence levels comparing the results of NPWT with those of conventional measures (evidence level 2b and 3; total 19 NPWT patients, comparison treatment: alginate dressing).<sup>395,396</sup> In these studies the NPWT group had significantly fewer dressing changes compared with the alginate group ( $p < 0.001$ ).<sup>395</sup> The time to full skin epithelialisation was significantly shorter in the NPWT group (median, 57 days) compared with the alginate group (median, 104 days;  $p = 0.026$ ). The authors concluded that this finding does not allow further inclusion of patients from an ethical point of view, therefore the study was stopped prematurely.<sup>396</sup>

The main statements in the published literature are:

- For high-risk surgical patients with a fully exposed infected prosthetic vascular graft, NPWT along with aggressive debridement and antibiotic therapy may be an effective alternative to current management strategies<sup>392,397,398</sup>
- To create the therapy concept, every infection after vascular procedure has to be individually evaluated
- Applying PVA foam directly to an exposed vessel or reconstruction is possible. Sometimes in a two-layer combination PVA foam is combined with polyurethane foam. Today, mostly PU foam is used over a small silicone dressing, a wound

contact layer, which protects the infected vessel or graft

- Low suction does not harm blood vessels or grafts. Mostly lower pressure levels of –50 to –100 mmHg are recommended to avoid bleeding and further damage of the affected vessel<sup>399</sup>
- Suction should be used in continuous mode rather than intermittently
- If possible, early coverage with muscle, for example sartorius myoplasty, is advantageous (exposed grafts cannot be covered with split-skin graft)
- Graft/patch salvage and complete wound healing was achieved in 82–91 % cases<sup>399–401</sup>
- The mean duration of NPWT was 14–43 days<sup>399–402</sup>
- The mean duration to achieve complete wound healing ranged from 24 (a study with sartorius myoplasty) to 51 days<sup>218</sup>
- Not evidence-based or literature-based, but very often discussed: graft infections without involvement of the proximal and distal anastomosis, the preservation of the graft may be attempted by NPWT, provided a contamination of the graft with *pseudomonas* is excluded
- Major complications of NPWT, such as severe bleeding, were not reported in studies when using NPWT with lower suction level. Regarding pain there are conflicting findings. Some authors reported significantly less pain<sup>395</sup> and others observed an increased need for analgesics in 1/7 of the patients<sup>401</sup>
- To prevent severe bleeding complications, when using NPWT directly in contact with the highly friable infected vessel walls or anastomoses, the patient should be treated only in the hospital

- Preventive use ciNPT significantly decreased the incidence of groin wound infection in patients after vascular surgery.<sup>403</sup>

To recap, NPWT in patients with deep peri-vascular groin Szilagyi II and III infections can be regarded as the dominant strategy due to improved clinical outcome with equal cost and quality-of-life (QoL) measures.<sup>395</sup> Even in the presence of synthetic vascular graft material, NPWT can greatly simplify challenging wound-healing problems leading to wound dehiscence and its sequelae.<sup>401</sup> NPWT without muscle flap coverage is considered to be safe within expert opinion and enables graft preservation in the majority of patients with minimal morbidity, no perioperative limb loss, or mortality. However, it should be mentioned that NPWT on vessels and grafts is outside the manufacturer's recommendations. The majority of infected grafts were preserved without reinfection during a mean long-term follow-up of seven years.<sup>400,404</sup> This treatment algorithm avoids major reconstructive surgery and should be used when dealing with Szilagyi III vascular infections.<sup>400</sup> For several authors, exclusion criteria for NPWT were an alloplastic graft infection with proximal expansion above the inguinal ligament, blood culture positive for septicaemia or septic anastomotic herald or overt bleeding.<sup>401</sup>

### Lymphocutaneous fistulas

NPWT can be used for the management of lymphocutaneous fistulae. The successful treatment of about 20 patients with lymphocutaneous fistulae of the groin has been reported in the peer-reviewed literature, as of end 2015, four case reports (level 5 evidence) and 2 case series (level 4 evidence, one review).<sup>405–410</sup>

Axillary and inguinal lymph node dissections as well as surgery of the infra-inguinal vessels can cause injury to efferent lymphatic vessels. This

can lead to lymphostasis or a lymphocele when the skin is intact or to a lymphatic fistula when a wound is present. A wide variety of therapeutic options have been developed in the past and range from the use of compression dressings to scab formation, the use of fibrin glue and, where possible, ligation of leaking lymphatic channels. NPWT is described here as a further non-invasive method of treating lymphocutaneous fistulas.

To date, the use of NPWT for the treatment of lymphocutaneous fistulae has been reported in only 19 cases (level 4 and 5 evidence).<sup>405–410</sup> The first report by Greer et al.<sup>406</sup> describes the treatment of a 49-year-old female patient with bilateral lymphocutaneous fistulae after aortobifemoral bypass and the treatment of a 77-year-old female patient who developed a fistula after evacuation of haematoma following femoral puncture. In both cases, it was possible to close the fistulae using NPWT alone. Unfortunately, the research group provides no information on the level of negative pressure and the type of suction that was used.

Steenvoorde et al. report a patient who underwent an ilioinguinal node dissection for a regional metastases melanoma.<sup>410</sup> Unfortunately, a deep wound infection occurred with extensive skin necrosis and production of abundant wound fluid (750 ml daily). Despite dressing changes six times daily, the wound deteriorated, necessitating further operative debridement. In theatre, the authors failed to identify the lymphatic fistula and therefore were unable to close it. Therefore NPWT was started. After 11 days of NPWT, the lymphatic leakage completely stopped. Concurrent successful management of the wound with split-skin graft therapy led to a complete closure of the wound. The treatment was not painful, dressing changes could be done in the ward, and there were no complications. The third group, Rau et al.<sup>409</sup> retrospectively investigated clinical and diagnostic data from eight patients (1995–2005) with penile

cancer and postoperative lymphocutaneous fistula. Of these eight patients, four were treated by NPWT. Their data show that, despite higher primary introduction costs, NPWT is advisable and resulted in a shortened hospitalisation and reduced overall costs per patient.

In a paper from Hamed et al. a duration of NPWT of 10–18 days up to closure of the fistula was reported. A successful wound healing was achieved in all patients with no recurrence after NPWT.<sup>405</sup>

Lymphocutaneous fistulae are rare complications of general and vascular surgery as well as of interventional radiology. They can, however, significantly lengthen hospital stays. The wide variety of treatment methods devised to date indicates that no one single method has been successfully used in a large enough number of cases. For this reason, NPWT is described here as an interesting alternative to other treatment options for this indication. Moreover, it appears necessary to consider and discuss the special level of NPWT and mode of suction that should be used in the management of lymphocutaneous fistulae. One of the advantages of NPWT is that it is a non-invasive method that can be used outside the operating theatre and can also be combined with surgical procedures such as the attempted ligation of lymphatic vessels or scab formation. Greer et al.<sup>406</sup> believe that granulation tissue grows as a result of NPWT and covers open lymph channels until the fistula is eventually closed. The key to success seems to be the tissue compression caused by NPWT. At first glance, this appears to be illogical since the application of suction can be expected to drain lymphatic vessels and thus to stimulate lymph flow. However, findings show that the foam is actually sucked into the tissue. This causes compression of the tissue at the pore walls and low suction in the area of the pores. It should also be borne in mind that the suction-induced reduction of foam size results in tension on the wound edges,



meaning that the tissue is further re-approximated and in a compression of the wound. These reflections suggest that a high level of negative pressure should be used in order to apply high local pressure to the tissue. Since a hyperaemic response with hyperperfusion and the reopening of closed vessels is not desired in the treatment of lymphocutaneous fistulas, intermittent treatment should not be used. Therefore, from the theoretical point of view, a continuous negative pressure of  $-200\text{mmHg}$  should be recommended.

NPWT can be used for the treatment of lymphocutaneous fistulae. The results of experiments support the assumption that the compressive effect of NPWT is the key to successful treatment. Within expert opinion, a high continuous negative pressure of  $-200\text{mmHg}$  appears to be effective for this indication.

## Non-healing wounds

Since the 1990's NPWT was applied to a number of chronic ulcerative conditions, including LUs, PUs and DFUs, and its adoption has increased constantly up to now.<sup>27,370,411</sup> For non-healing wounds, the mechanisms of action are removing fluid and exudates from the wound, relieving pressure, promoting perfusion and, at least until a certain extent, redistributing pressure in the wound bed. In the following sections the indications of NPWT for non-healing wounds will be presented in detail.

### Leg ulcers

LUs are open lesion of the lower leg due to arterial or venous insufficiency, or both, that can last months or even years. They affect as many as 5% of the general population and cost more than €2,000 per year per patient treated.<sup>412-414</sup> While the pathophysiology of arterial ulcers has been linked to the distal ischaemia, the relation to vein insufficiency is not completely understood;

peripheral oedema due to venous stasis has been evaluated as the major component of ulcer formation, and the most important aspect of the treatment are aimed in contrasting this.<sup>415,416</sup> Compression bandaging and local dressing are the cornerstones of therapy for VLUs.<sup>417-419</sup>

LUs have a high tendency to recur, which is why it might be helpful to focus on the underlying aetiological factors and the ulcerative and non-ulcerative phases, rather than on the treatment of the single incident.<sup>412</sup>

The probability of healing is inversely related to both size and duration of LUs. Ulcers smaller than  $10\text{cm}^2$  and that have existed for less than 12 months when first reported to a doctor have a 29% risk of not healing by the 24th week of care, while ulcers that exceed  $10\text{cm}^2$  and have existed for longer than 12 months before being reported have a 78% chance of not healing by 24 weeks.<sup>420</sup>

### NPWT in leg ulcers

As well as for almost all the others types of chronic wounds LUs were very quickly and intensively treated with negative pressure. The benefit that it could bring to a condition in which the main aetiological component was high interstitial pressure due to chronic oedema was immediately evident to most specialists in this field.<sup>163</sup>

Despite its popularity and the number of papers published in the last years on the use of NPWT in LUs, little evidence has been produced. In a recent Cochrane review<sup>421</sup> only one RCT satisfied the inclusion criteria among the 107 published articles selected.<sup>422</sup>

The RCT analysed included 60 patients randomised to NPWT or standard dressings and compression up to 100% granulation on the wounds. Following which, both groups received a skin-graft transplant, and those treated with NPWT had further 4 days of

negative pressure, while the others received only standard treatment.

There was low-quality evidence of a difference in time to healing that favoured the NPWT group. The study reported an adjusted hazard ratio (HR) 3.2, 95% CI: 1.7–6.2. The follow-up period of the study was a minimum of 12 months. There was no evidence of a difference in the total number of ulcers healed (29/30 in each group) over the follow-up period. This finding was also low-quality evidence. There was low-quality evidence of a difference in time to wound preparation for surgery that favoured NPWT [HR 2.4, 95% CI 1.2–4.7]. Limited data on adverse events were collected, providing low-quality evidence of no difference in pain scores and Euroqol (EQ-5D) scores eight weeks after surgery.

Due to the poor quality of the results the authors of the Cochrane review concluded that:

*'There is limited rigorous RCT evidence available concerning the clinical effectiveness of NPWT in the treatment of leg ulcers'*<sup>421</sup>

### Pressure ulcers

PU affect between 5% and 10% of hospitalised patients and are responsible for a significant decrease of the quality of life, increasing costs of treatment and delayed healing in the affected patients.<sup>423–425</sup> A PU is produced by shear stress, pressure or both over bony prominences and primarily affect insensitive patients, bedridden or those forced to be immobile. PUs are facilitated by malnutrition, chronic diseases, old age and acute or chronic reduction in skin perfusion.<sup>426–429</sup>

According to the European Pressure Ulcers Advisory Panel (EPUAP), PUs can be classified as grade I to IV— grade I being the least and grade IV the most severe.<sup>430</sup>

The management of PUs consists of the relieving

of shear and pressure from pressure points, the mobilisation of patients and the debridement of necrotic and non-viable tissue, plus local dressings, associated with systemic interventions, such as antibiotic therapy in case of infection or dietary supplementation in case of malnutrition.<sup>430</sup>

### NPWT in pressure ulcers

Despite its increasing diffusion among specialists, the use of NPWT in PUs is not yet supported by sufficient evidence. A recent Cochrane review demonstrated how little high-level evidence is published in this field.<sup>13</sup> This review included four studies selected from 82 records screened, and showed no differences between NPWT and traditional therapies for PUs. Furthermore, it did not provide any conclusive data on the possible advantages of such an approach in this field.<sup>431–434</sup>

Moreover, the quality of the study designs, the small amount of patients included and the possible biases identified by the Cochrane analysis would diminish any potential findings. For these reasons the authors of the review concluded that

*'This comprehensive review of current randomised controlled trial evidence has highlighted the current uncertainty regarding the effectiveness of negative pressure wound therapy (NPWT) as a treatment for pressure ulcers'*.<sup>13</sup>

Despite of this, NPWT is increasingly being used to manage PUs, most likely due to its flexibility, which allows the caregivers to insert it into a more complex and articulated therapeutic strategy. It is expected, for the near future, that better designed and dimensioned prospective trials will improve the evidence profile of NPWT for treatment of PUs.

### Diabetic foot ulcer

With a prevalence ranging between 5 and 10% of the general population, diabetes mellitus is the

most common chronic disease globally, and its prevalence is expected to increase up to fivefold in the next years.<sup>435,436</sup>

The complications of diabetes—both microvascular, like retinopathy, nephropathy and neuropathy, and macrovascular, like peripheral arterial disease and cardiomyopathy—can develop into clinical syndromes. Of these syndromes, DFUs represent the most important one, both in terms of prevalence, since they affect 15–20% of diabetic patients at least once in their life,<sup>437</sup> and in terms of severity, because they are the most frequent cause of lower limb amputations and are associated with a mortality that is higher than that of many types of cancer.<sup>438,439</sup>

Diabetic foot ulceration is defined as a wound that extends through the full thickness of the skin below the level of the ankle.<sup>440</sup>

The multifactorial pathogenesis, due to the contemporary presence of neuropathy and vasculopathy complicated by infection, explains the difficulties in management of DFUs. It also explains the tendency of recurrences, which differentiate DFUs from the other types of chronic ulceration. It has been estimated that only one third of neuropathic DFU, adequately treated, heal in 20 weeks, and that up to 70% recur in 5-year follow-up time.<sup>441,442</sup>

The treatment of DFUs is complex and aims to address all the relevant components that generate and sustain the non-healing wound.<sup>440,443</sup> Offloading, debridement, revascularisation, systemic antibiotic therapy are the cornerstones of treatment.<sup>444</sup>

### NPWT in diabetic foot ulcers

In 2004 the first guidelines for the use of NPWT for DFUs management were published.<sup>445</sup> The rationale for adopting NPWT in DFUs was related to its capacity of removing exudate, protecting

the wound from exposure to the environment, reducing odour and helping debridement.

The use of NPWT in DFUs has a large span, from postsurgical lesions where NPWT is applied to facilitate wound closure by secondary intention to non-healing neuropathic or neuro-ischaemic ulcers. In both cases possible ischaemia and infection must be addressed before applying NPWT.

However, the evidence for the effectiveness of NPWT in DFUs is sparse, as demonstrated in a recent Cochrane review.<sup>14</sup> From 477 articles screened, 20 were evaluated for eligibility, and 5 met the inclusion criteria.

Of the five RCTs included in the analysis, three collected data for less than 100 patients, and their results were evaluated as inconclusive based on the data given by the remaining two RCTs.<sup>446–448</sup> Hence, the review is based on two well-dimensioned RCTs. Armstrong et al. compared NPWT with moist dressings in postsurgical DFUs,<sup>9</sup> while Blume et al. compared NPWT with a variety of dressings in the management of non-healing DFUs.<sup>10</sup>

Armstrong et al. included 162 consecutive diabetic patients with postsurgical foot wounds due to forefoot amputations, which were randomised to NPWT versus moist dressings and followed for 16 weeks; both healing rates, healing time and number of amputations were evaluated as outcomes of this trial. There was a statistically significant increase in the number of wounds healed in the group treated with NPWT (43/77; 56.0%) compared with the moist dressing group (33/85; 38.8%), with a probability of healing which was 1.44 times higher in NPWT compared with the control group [RR: 1.44; 95%CI: 1.03–2.01]. Healing time, defined as the time to complete wound closure, was significantly shorter in the NPWT group (median time-to-healing: 56 days) compared with the moist dressing group (median: 77 days;  $p < 0.005$ ); the

probability to heal, in any given point during follow-up was 1.99 times higher in NPWT group.

There were five major amputations in the moist-dressing treated group, while none occurred in the NPWT group. Considered altogether, major and minor amputations were 2/77 (3%) in the NPWT group and 9/85 (11%) in the control group; the difference was not significant [RR: 0.25, 95% CI: 0.05–1.10].<sup>9</sup>

No differences in adverse events—NPWT 40/77 (52%), controls 46/85 (54%) [RR: 0.96; 95% CI: 0.72–1.28]—were observed between the groups.

Blume et al. included 342 patients with DFUs of different aetiologies.<sup>10</sup> These were randomised into two groups: one was treated with NPWT, the other with moist dressings, both as additions to standard care. The patients were followed for 16 weeks and healing rates, healing times and amputation rates were compared at the end of the period.<sup>10</sup> There was a statistically significant increase in the number of wounds healed in the NPWT group (73/169; 43.2%) compared with the moist dressing group (48/166; 28.9%). Healing time was significantly shorter in the NPWT group, with median time-to-healing of 96 days [95% CI: 75.0–114.0], compared with the moist dressing group, in which the median number of wounds healed was not reached during 16-week follow-up. The study reported a statistically significant ( $p=0.035$ ) reduction in the number of amputations in the NPWT group (4.1%) compared with the moist dressing group (10.2%).<sup>10</sup>

Although on different indications, postsurgical wounds and chronic DFU, the results of the two large RCTs are unequivocal and demonstrate how NPWT may be safe and effective in the management of DFUs. Nevertheless, some aspects related to the characteristics of the studies and of the time when they were conducted deserve some consideration.

In the study by Armstrong et al.<sup>9</sup> the possibility of converting patients to surgery was left to the judgement of investigators and Blume et al.<sup>10</sup> had a high drop-out rate in both groups. These factors led the authors of the Cochrane review to conclude that the studies could be at risk of bias and that any change in NPWT practice would need to be informed by clinical experience and should acknowledge the uncertainty around this decision on account of the quality of data.<sup>14</sup>

Moreover, the technological evolution and new methods such as instillation that have emerged after the conduct of these two studies (2005 and 2008) are believed to have changed the scenario. With these limitations, NPWT represents an important adjuvant therapy in the management of DFUs, and its diffusion is increasing among the specialists, or for the increasing possibility of applying it in the multi-dimensional management strategy of DFUs, which is complex and needs different approaches modulated according to the stages of the pathology.

The use of NPWT has also been described as a possible treatment strategy for other areas such as palliative treatment of wounds, necrotising fasciitis, dermatology for example pyoderma gangraenosum<sup>239</sup> and neurosurgery.<sup>449,450</sup>

## Cautions and contraindications

The following contraindications of NPWT have been established:<sup>451,452</sup>

- Clotting disorders (risk of bleeding) and acute mild to moderate bleeding in the wound region after injury/debridement
- Exposed organs, vessels and vascular anastomoses, which might be altered or damaged by NPWT
- Necrotic wound bed

- Untreated osteomyelitis
- Neoplastic tissue in the wound area.

### Risk of bleeding

If there is manifest bleeding or a risk of bleeding, NPWT must not be applied to the wound. In these cases, suction could result in a continuous removal of blood leading to significant blood loss.<sup>453</sup> Some commercially available negative pressure systems are fitted with a collection canister with a volume of 300–500 ml and also have an audiovisual alarm to alert the provider or patient if the canister is full. Blood loss can thus be prevented in time. Additionally the bleeding can clot the foam and therefore stop any function of the NPWT device.

### Exposed vessels and vascular prostheses

Recent practical experience and theoretical knowledge have shown that the use or non-use of NPWT for the treatment of exposed vessels and vascular anastomoses should be reconsidered and discussed. Over the last 15 years, there has been an increasing number of publications by different authors who investigated the use of NPWT in infected inguinal wounds after vascular surgery.<sup>390,391,393,454–457</sup> In some cases, pieces of foam were placed directly into the infected wound over the exposed vessel or the vascular anastomosis. In these studies, NPWT neither compromised circulation nor caused any other complications.

### Necrotic wound bed

Necrotic tissue acts as a barrier to new tissue growth. The use of NPWT must therefore be preceded by radical debridement.

### Untreated osteomyelitis

Due to the deep extension of a potential osteomyelitic focus, simple surface treatment is unlikely to be successful, even if direct contact between the dressing and the bone is ensured. In this case, treatment must include the radical

removal of the focus of infection. Instillation therapy is another option to be considered in these cases.<sup>36,37</sup> However, this is considered outside manufacturers' recommendations.

### Malignant wounds

NPWT is known to promote granulation tissue growth and is therefore used for the purpose of improving tissue perfusion and enhancing granulation tissue formation. As a consequence, it should not be used in the presence of malignant neoplastic tissue.<sup>458</sup> The consensus paper<sup>458</sup> and other publications in the literature, as well as our own experience, suggest that NPWT can be useful as a purely palliative measure in inoperable cases, for example, patients with a gangrenous tumour or with a malignant cutaneous metastatic wound.<sup>458,459</sup> Particularly in patients with tumours that are not completely resectable or with ulcerating lesions or highly exudative wounds, NPWT should not be strictly regarded as contraindicated. When used as a purely palliative measure, it allows wounds to be covered in a hygienic and clean manner and at the same time is more comfortable and less painful for the patient without restricting any remaining mobility. In special cases, the presence of malignant tissue in the wound bed can thus be considered an indication for NPWT.<sup>460,461</sup>

## NPWT and instillation

NPWTi is a further development and modification of conventional NPWT for the complementary management of acute and chronic wound infections after initial surgery. The first publications date from the year 1998.<sup>36</sup> To date, there are 104 peer-reviewed articles that have been published on the subject of NPWT in combination with instillation; keywords: 'instillation', 'instill', 'irrigation'; as of 31 December 2015 (appendix 2) and nine studies comparing NPWTi with NPWT or standard therapies (appendix 9).

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## Functional principle NPWT with instillation

This modification of the conventional NPWT involves the retrograde instillation of an antiseptic or antibiotic substance (for example, pyrrolidinone homopolymer compound with iodine, octenidin dihydrochloride) into the sealed wound.<sup>462</sup> Between 1999–2012, several refinements in equipment have provided the option of automatically controlled instillation therapy. This permits constantly controlled instillation without burdening either the patient or the nursing staff. Using today's computer-controlled programmable therapy units it is possible to automatically control the instillation therapy, including the amount of fluid, duration of instillation, soak time, frequency of this therapy cycle. NPWTi has been successfully used for adjunctive management of acute wound infections after surgical wound debridement.<sup>35,37–41,463,464</sup> Several studies suggest that even non-infected wounds show a benefit in healing when treated by NPWTi using saline solutions in comparison to conventional NPWT or standard moist wound treatment.<sup>42,43,465</sup>

## Methods of action

Instillation therapy is performed during NPWT by instilling the desired solution into the foam via a dedicated tube system and then, after a set time during which the solution is left to take effect and no suction is applied, removing the solution by suction (continuation of the NPWT). In principle, this alternation between NPWT and instillation periods can be repeated as often as desired. In fact, the instillation should be performed several times a day for a sufficient antimicrobial effect for example. This should be done according to a controlled time sequence: Instillation period of the solution (saline, antiseptic or antibiotic solution; approximately 10–30 seconds), dwelling period (dependent on the time the solution need to be effective, e.g. 20 minutes) – suction period (e.g. 2–3 hours).

The first phase (instillation phase), lasts for approximately 10–30 seconds, the vacuum line closes, the instillation line opens and the instillation fluid moves through the first tubing to saturate the foam and bath the total wound. During instillation, pressure values above the atmospheric ambient pressure are eventually reached in the foam and in the wound region. The wound surfaces are then completely in contact with the instilled solution. During the first instillation, the intake of the inflowing liquid by the foam and the expansion of the foam are monitored through the transparent drape. The amount of fluid required for this phase is entered in the software-supported instillation system (for example, 75 ml).

After the closure of the instillation line, the in- and outflow remain blocked in the subsequent second phase, the wound cleansing phase. The instilled solution has unhindered access to the wound surface, even in deep and piercing wounds. The duration of the active phase is variable, for antiseptic based on the pharmacodynamics of the fluids used, dwell time is usually 5–30 minutes.

When the third phase—the vacuum phase—begins, the original negative pressure is restored. At the same time, the solution is removed by suction together with the wound exudate and the wound detritus. The duration of the vacuum phase is dependent on the clinical assessment of the virulence of the infection and the associated toxin production, and on the viscosity of the wound exudates that affect the porosity of the foam. This phase takes between 30 minutes and several hours; the standard setting is one to three hours.

Each instillation cycle corresponds to a normal dressing change. However, with the modern computer-controlled instillation system, the number of 'dressing changes' is practically unlimited, so that an uninterrupted intensive and effective wound management becomes possible.

For both patient and therapist, the number of time-consuming and often painful dressing changes is substantially reduced. Instillation therapy thus appears to be a patient-friendly and cost-effective form of management for acute and chronic infected wounds. Above all, it is the automation of the therapy unit that ensures the safety, effectiveness and treatment comfort of the procedure. On the NPWT unit, the therapy unit contains an integrated collecting reservoir for the instillation fluid that is removed by suction.

### NPWTi versus irrigation-suction drainage

Instillation therapy should not be confused with the irrigation-suction drainage described by Willenegger<sup>466</sup> in which a continuous directional flow of liquid is generated that naturally takes the shortest route along a pressure gradient between the inflow via the infusion line and the outlet via the drainage tube. With irrigation-suction drainage, it is generally believed that dead spaces are created in the neighbourhood of these 'irrigation routes'. These dead spaces can no longer be reached by the irrigation solution after a few irrigation-suction cycles and may thus persist as septic 'islands'. With instillation therapy the wound is, ideally, completely filled by the foam so that the creation of 'dead spaces' is unlikely.

### Indications for NPWTi

Current experience in the application of instillation therapy includes the following indications for its use:

- Septic wounds: soft tissue after initial surgical debridement (acute infections, particularly postoperative infections, are considered the most favourable indications for NPWTi), osteitis, osteomyelitis (chronic soft-tissue and bone infections after surgical removal of the septic focus)
- General surgery: abdominal sepsis, extensively

drug-resistant bacteria wound infection after liver transplantation (however, off label if following open abdomen)<sup>467,468</sup>

- Thoracic surgery: para- and post-pneumonic pleural empyema, bronchopleural fistula with thoracic empyema, mediastinitis after cardiac surgery (however, this is off label)<sup>469-472</sup>
- Severe periprosthetic infection in breast reconstruction<sup>473</sup>
- Trauma and orthopaedics: High-energy complex fracture, acute complex wounds of the lower extremities, endoprosthetic infections and high-pressure injection injuries, infection in the region of the implant bed (in many cases, asepsis was achieved even without removing the osteosynthesis material).<sup>474-479</sup> However, treatment of these kinds of wounds may be limited due to the risk of fluid retention
- Necrotising fasciitis and gas gangrene.<sup>480-482</sup>
- Chronic wounds such as diabetic lower limb ulcers VLU, PUs<sup>483-489</sup>
- Uncomplicated wounds, where instillation therapy can regenerate the porosity of the foam, which preserves the effectiveness of the seal and extends the intervals for vacuum dressing changes. With aseptic wounds, Ringer's solution can be used for instillation to increase granulation tissue formation (appendix 9).<sup>252,488,490</sup>
- Painful wounds (postoperative wounds or infection-related conditions of pain occasionally might benefit from the instillation of local anaesthetics; this can also be an option when a painful PU dressing change is anticipated).<sup>491</sup>

### Fluids for NPWTi

Most often the time of NPWTi was 7–14 days,

however, one author group used NPWTi for up to 3 weeks.<sup>492</sup> The following use of NPWTi using different fluids for instillation (some within and some outside the manufacturers' recommendations):

- 0.9% normal saline: mean duration of NPWTi for 12 days, 4 cycles per day, dwell times of either 5 or 60 minutes<sup>43,493–495</sup>
- Polyhexanide: 0.02% or 0.04%, 20 minutes dwell time, for 4–8 days, 4–8 cycles per day.<sup>474,495–500</sup>
- Octenidine-based irrigation solution: 3 minute dwell time, for 4–8 days, 2 cycles per day.<sup>462,501</sup>
- Acetic acid solution: 1% solution, 20 minutes dwell time, for 4–8 days, 4–8 cycles per day<sup>497,502</sup>
- Super-oxidized water: repeated every 2–4 hours with a 5–10 minute soak time<sup>483,503</sup>
- Dakin's solution: 10 minutes every hour, diluted 12.5% for 10 days<sup>503,504</sup>
- Potassium permanganate solution: 1:5000<sup>505</sup>
- Antibiotic solution: such as doxycycline, colistin and rifampicin<sup>36,468,506,507</sup>
- Insulin<sup>508,509</sup>

NPWTi is increasingly used as an adjunct therapy for a wide variety of acute and chronic wounds. In the last ten years, particularly, NPWTi has played a role in the adjunctive management of postoperative infected wounds. The use of instillation has enabled conventional NPWT to be extended in these difficult situations by using antiseptic and antibiotic solutions. Nevertheless, the literature shows that the role of NPWTi continues to expand and can be used today also in the management of both acute and chronic non-

infected wounds to support wound-healing, mostly by instillation of saline.

Despite its growing popularity, there is a paucity of evidence and lack of guidance to provide effective use of this therapy. Available evidence relating to the use of NPWTi in acute and chronic wounds is promising but limited in quality, being derived mostly from case series or small retrospective or prospective studies. Nevertheless, the available studies show that NPWTi is an effective treatment protocol. It has been shown to help reduce healing time, promote long-term functional and positive cosmetic outcomes in debilitated patients with severe complex clinical situations, and potentially help expedite wound closure.

The overview and literature analysis suggest that NPWTi is, in certain clinical situations, more beneficial than standard NPWT for the adjunctive management of acutely and chronically infected wounds that require hospital admission.<sup>488</sup>

Additionally, there are clinical observations that NPWTi by saline is more effective in wound healing than NPWT alone, creating the question in which indications principally NPWTi-saline should be given and when not. As a future direction it should be scientifically clarified and evaluated in terms of cost-effectiveness, whether all non-infected wounds should be treated by NPWTi-saline.<sup>270,510,511</sup>

## ciNPT

In industrialised countries, SSIs occur in general surgery in about 5% of patients and in high-risk surgical procedures reaching over 50% lengthening the average length of stay of 12.6 days.<sup>512</sup>

SSIs burden patients, their families, the health-care system, and society with loss of productivity, prolonged hospital stays, increased health-care



provider visits, and increased financial costs. With a mortality, e.g. in cardiovascular surgery of up to 50%, DSWI, are a rare but devastating complication after median sternotomy for cardiac surgery.<sup>513</sup>

Current standards of care for preventing SSIs include the implementation of defined procedures and standardising processes using preoperative prophylactic systemic antibiotics, preoperative soap or antiseptic shower/bath, aseptic incision site surgical preparation and sterile and meticulous surgical technique. Thus, several author groups try to reduce the SSI rate by new incision devices (like cold-plasma scalpel), new suture techniques and products including disposable electrocardiogram leads and pacing wires, antibiotic-coated sutures, and silver-impregnated dressings, wound irrigation and iodine-impregnated skin drapes. Additionally, some authors tried to reduce the DSWI rate by the implementation of comprehensive, multidisciplinary wound management team. Yet, the continued high SSI rates in surgery demonstrate the need for further preventative methods. Traditionally, surgeons have closed surgical incisions with primary intention using sutures, staples, tissue adhesives or a combination of these methods. Now, surgeons from several disciplines have recently discovered that NPWT applied over closed incisions can also be beneficial in preventing incision complications. The term ciNPT refers to any type of NPWT using fluid-absorbing dressings over closed incisions.

#### Literature review: randomised trials

Since 2004, numerous published studies have reported improved incisional outcomes using ciNPT across all surgical disciplines. Against this background, we analysed the available DSWI and ciNPT in surgical incision management. Our goals were to determine whether and how ciNPT is beneficial in preventing wound incision complications and then to formulate recommendations for potential indications for use.

The search covered papers published in the period from 1 January 2000 to 31 December 2015. The keywords included: 'prevention', 'negative pressure wound therapy', 'NPWT', 'active incisional management', 'incisional vacuum therapy', 'incisional negative pressure wound therapy', 'incisional NPWT', 'incisional wound vacuum assisted closure', 'closed incisional negative pressure therapy', 'wound infection'. A limited number of robust, prospective, randomised, comparative, controlled studies on ciNPT use over closed surgical (all surgical disciplines) incisions that might most benefit from this therapy exist. The literature search identified 116 (appendix 7). Since 2009, several RCT's (n=7) and meta-analyses (n=3) have described the effect of NPWT on closed incisions in all surgical fields (table, appendix 10). These studies encompass various wound types and surgical interventions, including high-risk open fracture types (tibial plateau, tibia, pilon, calcaneus), total knee replacement procedures, lower extremity amputations and elective, open colorectal resection. Enrolled patients often had comorbidities, including obesity (BMI  $\geq 30$  kg/m<sup>2</sup>), diabetes mellitus, peripheral vascular disease, or chronic obstructive pulmonary disease. The two studies reported no differences in SSI rates or dehiscence between ciNPT and control (silver impregnated wound dressings or sterile gauze dressings) groups.<sup>366,514</sup> Of these one study was stopped prematurely due to blister formation in a majority of ciNPT group patients.<sup>515</sup>

The most recent meta-analysis performing an evaluation of the effectiveness of ciNPT in lowering the incidence of SSI compared with standard dressings was based on a literature search, which was conducted to find all publications (not only RCT's) comparing ciNPT with standard incisional care.<sup>516</sup> This study used fixed-effects model to assess between-study and between-incision location subgroup heterogeneity and effect size. Additionally funnel plots were used to assess publication bias. The

authors demonstrated an overall weighted average rates of SSI in the ciNPT and control groups were 6.61% and 9.36%, respectively (relative reduction in SSI rate of 29.4%). Furthermore, the authors could show that the odds of SSI decrease was 0.496 ( $p < 0.00001$ ).<sup>516</sup> Overall rates of dehiscence in ciNPT and control groups were 5.3% and 10.7%, respectively. The results of this meta-analysis suggest that ciNPT is a potentially effective method for reducing SSI and may be associated with a decreased incidence of dehiscence.

### Mechanism of action of ciNPT

There are a number of articles that deal specifically with the mechanisms of action of NPWT over closed incisions.<sup>517-521</sup> The evidence supports the hypothesis that reduction of lateral tension and haematoma or seroma, coupled with an acceleration of the elimination of tissue oedema, are the main mechanisms of action of incisional NPWT.

### Lateral tension

NPWT on closed wounds seems to reinforce the wound by reducing the lateral tension in suture lines. The wound will then gape less and the risk of scarring may decrease. Reductions in lateral tension have been demonstrated during NPWT with computer modelling and *in vitro* measurements.<sup>517</sup> There is similar data that non-NPWT mechanical forces can stress-shield closed incisions and reduces scarring.<sup>521</sup> There is also evidence from animal studies that the breaking strength of wounds is increased through the application of continuous NPWT to closed incisions.<sup>518</sup> Bolstering oppositional forces at the incision through reduction of lateral tension improve scar cosmesis.<sup>522</sup> Collagen synthesis and its organisation are influenced by mechanical stimuli.<sup>523,524</sup> Furthermore, the transformation from fibroblasts to myofibroblasts is affected by mechanical stimulation<sup>525</sup> and they play an important role in producing excess extracellular matrix<sup>526</sup> and thus in the hypertrophic scar

formation.<sup>527xx</sup> In this way, the therapies involved in the decrease of myofibroblasts numbers might potentially have a positive effect on scar cosmesis and thus in functionality.<sup>517</sup>

### Tissue perfusion

There are few reports on ciNPT on the effect of perfusion adjacent to closed incisions. An experimental study shows that while conventional NPWT affects perfusion in defect wounds, there is little effect on perfusion in incisional wounds.<sup>44</sup>

### Oedema

An experimental study in pigs indicated an effect by NPWT over closed incisions in oedema. The results from studying how radiolabel microspheres are cleared to lymph nodes beneath incisions treated with NPWT suggested increased lymphatic drainage.<sup>520</sup>

### Haematoma and seroma

Collections of blood and serum in sub-incisional tissues create dead spaces that may predispose the patient to infection. NPWT over closed incisions has shown to result in reductions in haematoma volume.<sup>518,520,528</sup> This has also been demonstrated clinically for seroma in a small RCT.<sup>529-531</sup>

### Reduction of surgical site infection rate

Infection of the wound has been indicated (for the first time in 1994) as the aetiological cause of the 'delayed healing of the wound'.<sup>532</sup> By reducing seroma and haematoma formation the risk of wound infection might also decrease as the wound can heal without a persisting open entrance for bacteria. Haematoma are thought to serve as rich nutrient sources for infection.<sup>533</sup> Wound infection leads to tissue breakdown and then surgical wound dehiscence, through interference with normal cellular mechanism of wound healing and devitalisation of underlying tissue.<sup>534</sup> Some authors pointed out a lower incidence of SSI<sup>450,534</sup> after

ciNPT in cardiac surgery,<sup>380,382</sup> and orthopaedic surgery.<sup>535</sup> However, none of these studies had a control group for comparison. Other studies with a control group also reported a lower incidence of SSI in colorectal surgery,<sup>536–541</sup> caesarean section,<sup>542–545</sup> total ankle arthroplasty,<sup>546</sup> abdominal wall reconstruction,<sup>547</sup> spinal surgery,<sup>450</sup> groin vascular procedure<sup>403</sup> and in CABG.<sup>379,383,548</sup> Stannard et al. in 2006 reported in a pilot prospective RCT no significant difference between the ciNPT group and control group in terms of infection or wound dehiscence.<sup>160</sup> The same group, in 2012, reported the results of a multicentre prospective randomised trial on a greater number of patient with the same characteristics stating that the incidence of infection and dehiscence was lower in the ciNPT group.<sup>528</sup> Masden reported a RCT in which there was no statistical difference in the incidence of infection and surgical wound dehiscence (SWD) between the ciNPT and comparative dressing groups.<sup>514</sup> In another study no difference again in surgical wound complication for abdominal wall reconstruction incisions has been reported.<sup>549</sup>

### ciNPT systems

The technology of ciNPT has recently been developed to involve the application over surgical incisions. Special wound dressings have been are designed to be applied over closed incisions. These are made of a material that has high-skin compatibility, such as a silicone adhesive. Wound fillers such as foam or gauze should not be applied directly on intact skin. The ciNPT systems described in the literature today (2017) are represented by:

- A polyurethane foam placed over the length of the incision, secured with a protective occlusive tape and attached to a commercially available NPWT device set at between  $-75$  mmHg and  $-125$  mmHg, in a continuous suction. Using this system, the surgeon can decide how long the ciNPT system should be on the incision, for

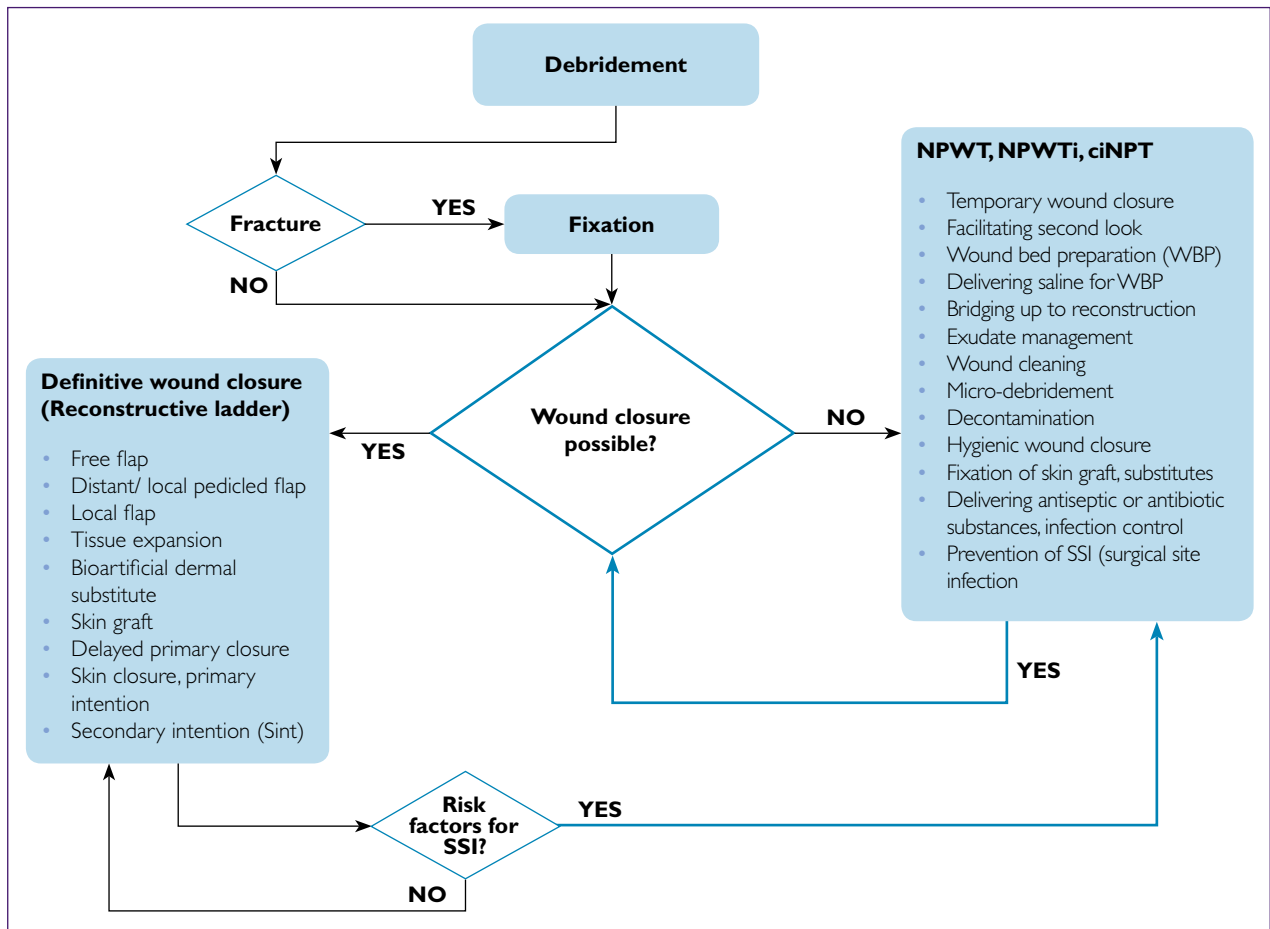
example, seven days or up to the removal of the sutures

- An integrated, one-piece dressing comprised of a polyurethane film with acrylic adhesive that provide adhesion of the dressing to the surrounding skin of the incision and a polyurethane shell that encapsulates the foam bolster and interface layer, providing a closed system. The dressing is connected to the small and portable single-use battery-powered NPWT device with a canister of 45 ml that produces a continuous negative pressure of  $-125$  mmHg for seven days
- A portable single-use canisterless device with a dressing composed of a silicon contact layer to minimise pain of removal, an airlock layer that allows even distribution of negative pressure across the dressing, an absorbent layer that moves exudates away from the wound, and a high moisture vapour transmission rate top film. The dressing is connected to a ultra-portable single-use system, with a continuous negative pressure of  $-80$  mmHg for seven days.

Overall, a majority of these case studies reported that ciNPT use was associated with decreases in wound complications, wound dehiscence, haematoma/seroma formation and reduction in SSI. To conclude from the experience to date:

- ciNPT is used in many different surgical disciplines: trauma and orthopaedic surgery, plastic surgery, general surgery, colorectal surgery, hernia repair surgery, post-bariatric surgery, thoracic and cardiovascular surgery, vascular surgery, obstetrics and urology
- The present state of knowledge is that there is no rationale to apply ciNPT to all surgical incisions because the costs are too high in comparison with that of standard dressings<sup>366,550</sup>

**Fig 3. The new algorithm in the treatment of wounds when using NPWT. Change from the old FIX (if there is a fracture) and FLAP (to close the wound) concept to the new FIX-NPWT-FLAP concept (if the wound closure will be not possible).<sup>552, 553</sup> The right box (NPWT, NPWTi, ciNPT) shows different purposes of the NPWT**



- Therefore, every surgical discipline or the scientific societies of various surgical specialities have to create a risk profile of operation and patient-related risk factors for surgical wound complications and then determine a cut-off marker for the decision to apply ciNPT.

### When to start, when to stop (achieved endpoint)

When delayed reconstruction is inevitable, radical

debridement is performed first, then NPWT is used as bridging therapy, and free flap could be considered for definite soft tissue coverage.<sup>551</sup> To date, there are no published recommendations in the literature about the best timepoint to start or stop NPWT. Searching with the keywords ‘interval’, ‘timepoint’, ‘time’, ‘delay’, ‘start’, ‘stop’, ‘end’ the only information found was about possible delays and allowed time intervals between primary wound debridement and the definitive closure by methods of the reconstructive ladder. There is no detail about the best timepoint to start

NPWT if wound closure is not possible and no information how long the treatment will be useful (Fig 3). Additionally, there are no evidence-based time intervals specifying when NPWT should be changed after initial placement in such cases, however, manufacturers instructions specify 48–72 hours between dressing changes.

Nevertheless, based on the available experience, some published data and recommendations of the manufacturer, it is possible to make a differentiation of the start and stop timepoints, duration of the therapy and sensible dressing change intervals between the different purposes of the NPWT (Table 1).

Sometimes, reconstruction in high-risk patients with severe lower extremity injuries will be delayed due to the patients' critical condition, advanced age, medical comorbidities, heavily exuding wounds and questionable viability of soft tissues. In these situations, NPWT will be an adjunct to delayed soft tissue reconstruction in patients with complex lower limb trauma, with NPWT bridging up to reconstruction.<sup>298</sup> But how long can this time delay be between initial debridement and the closure of the wound bridged by NPWT? The study showed evidence to support NPWT beyond 72 hours without increased infection rates and to support a reduction in flap rates with NPWT.<sup>262</sup> However, one author group showed that NPWT

**Table 1. Recommendations for starting and stopping timepoints of NPWT in different settings of NPWT-use**

Purpose of NPWT	Start	Stop	Dressing change intervals
Temporary wound closure (TWC) (based on: exudate management, micro-debridement and decontamination)	NPWT: immediately after debridement	ASAP up to wound closure (ReconLadder) or Slnt	2–4 days
Facilitating second look		ASAP, up to starting with WBP, TWC	If contaminated <48 hours
Wound bed preparation (WBP)		ASAP, up to wound closure (ReconLadder) or Slnt	3–4 days
Delivering saline for WBP		ASAP, up to wound closure (ReconLadder) or Slnt	3–4 days and in some cases 5–7 days*
Bridging up to reconstruction		ASAP–wound closure (ReconLadder), if possible within 7 days	3–4 days
Hygienic wound closure		ASAP - wound closure (ReconLadder)	3–4 days
Fixation of skin graft or skin substitutes (Integra, Matriderm)	NPWT: after skin transplantation	5–6 days, artificial skin substitutes up to 10 days	No planned dressing change
Delivering antiseptic or antibiotic substances	NPWT: immediately after debridement, initial wound care	Up to wound closure, vital and clean wound bed, total bacterial clearance not necessary	5–7 days
Prevention of SSI	ciNPWT: immediately after closure of incision	Between 7 days and timepoint to remove stitches (e.g. 12 days)	No planned dressing change
ASAP—as soon as possible, SSI—Surgical site infection, Slnt—Secondary intention: *Most companies recommend 2–4 days			

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may help reduce the flap size and need for a flap transfer for type IIIB open tibial fractures and that prolonged periods of NPWT usage, >7 days, should be avoided to reduce infection and amputation risks.<sup>554</sup> Other authors support this algorithm. They showed that patients who underwent definitive coverage within 7 days had a significantly decreased rate of infection (12.5%) compared with patients who had coverage at 7 days or more after injury (57%) ( $p<0.008$ ).<sup>555</sup> They concluded that the routine use of NPWT with severe open tibia fractures is safe and provides a good primary dressing over open wounds, but NPWT does not allow delay of soft-tissue coverage past 7 days without a concomitant elevation in infection rates.<sup>555</sup>

The result of a retrospective analysis shows the flap reconstructions performed beyond the frequently quoted critical interval yielded similar results to those of immediate reconstruction within the first 3 days, as reported in the literature. This strategy may reduce the importance of emergency reconstructions,

especially in polytraumatised patients.<sup>556</sup> This group of patients had been referred from a trauma centre at a mean interval of 19 days (range: 1–96 days) after the trauma event with temporary NPWT (purpose: bridging to reconstruction and wound bed preparation) on their wounds after initial fracture fixation and initial debridement of necrotic tissue. Flap reconstruction was thus only possible later than 72 hours and definitive reconstructive wound closure was achieved at a mean time of 28 days (range: 3–106 days). In clean and vital wounds a 7-day interval between dressing changes during NPWT for open traumatic fractures was shown to be acceptable.<sup>252</sup>

Against the background of the lack of high-grade evidence-based recommendations, it has to be formulated that NPWT in all NPWT-settings should start immediately. There are no reasons to delay. Additionally, there is no controversy to follow with NPWT for 10–14 days (except for fixation of skin graft where 5–6 days is recommended). But every use of NPWT must be able to be justified in the treatment team.

# 6. Patient perspective

This chapter describes the patient perspective of being treated with NPWT. The literature presents varying results with both negative and positive impact on the patient's QoL. NPWT affects the patient's life in all aspects, physical, psychological and social. The patient perspective may be described either qualitatively (as the patient's lived experience) or quantitatively (in measuring the patient's QoL in different domains of daily living).<sup>557</sup>

Patients undergoing wound treatment have different focuses, concerns, and needs related to treatment modality. Patients treated with NPWT have experiences that differ from the experience of patients treated with conventional treatment with dressings. The knowledge of these unique features of the experience of patients treated NPWT is required for the possibility to perform individualised care, which is the goal of all health care.

In the clinical use, NPWT has sometimes been viewed as a 'simple dressing', which could be considered as ignorance of the risks and safety issues with the treatment. This phenomenon is also seen in regards to the impact the treatment has on the patient. The patient treated with NPWT is dependent on a medical device for optimal health. NPWT is not a completely safe treatment and there are adverse effects. Therefore, it is important to focus on the patient's experience and to empower them in coping with the treatment so that the treatment itself does not become worse than the wound.

## Overall quality of life

The concept of QoL is defined as those aspects that can be clearly shown to affect health, either physical or mental health.<sup>557</sup> QoL can be measured by two basic approaches: generic instruments that provide a summary of QoL in general terms, and disease- or condition-specific instruments that are adapted to different diseases or conditions.<sup>558</sup>

Only a handful of studies have quantitatively assessed how the patients rate their QoL while being treated with NPWT and the literature presents varying results with both negative and positive impact on the patient's overall QoL. The majority of the studies show higher QoL estimation with patients treated with NPWT compared with those treated with traditional dressings. This result could be explained as being due to patients treated with NPWT experienced less pain, promotion of wound healing and subsequent faster discharge from hospital.<sup>559</sup> In a pilot study comparing overall QoL over a 12-week period, no statistically significant difference between patients treated with NPWT and with traditional dressings was noticed. The patients treated with NPWT, however, rated their social functioning higher after two weeks treatment. The authors of the study suggest this improvement may be due to methodological issues of the study such as small sample size and no baseline data.<sup>560</sup>

Treatment with NPWT does not seem to worsen the patient's overall experience in QoL, however research shows that in some domains, the patients do rate their QoL lower. It is especially in physical

functioning that the patients express deterioration in QoL, sometimes severe enough that the treatment must be terminated.<sup>561-563</sup>

## Physical aspects

### Pain

Pain is a common symptom for patients going through wound treatment.<sup>564,565</sup> The literature shows diverse experiences of pain in patients treated with NPWT. Some studies imply that patients treated with NPWT experience much pain with difficulties coping with regular pain killers.<sup>236</sup> While other studies show no significant differences compared with regular dressings or that NPWT seems to reduce the patients' levels of pain.<sup>236,395</sup> Research showed that patients treated with NPWT have a huge focus on the machine and its functioning, an explanation could perhaps be that this focus is overshadowing the patients' pain experience so that they do not perceive the pain in the same way as if they were to be treated with traditional dressings instead.<sup>566</sup>

The literature shows that some procedures in the wound treatment process are more painful than others especially during removal of the wound filler, particularly foam, and when applying the negative pressure.<sup>236,567</sup> To cope with the problem of pain during dressing removal lidocaine may be injected retrograde up the suction tubing into the wound filler before removal the pain experience of the patients has shown to be reduced in this way.<sup>236,241-243</sup>

It is described in the literature that usage of regional pain blocks may be an effective way of managing pain when patients ask for terminating the treatment due to severe pain burden.<sup>568</sup>

Another way to manage pain during treatment could be to choose gauze or PVA-based foam (white foam). It has been suggested that there is evidence for choosing these kinds of wound fillers to reduce

pain<sup>139,187,188</sup> probably due to less ingrowth of tissue in the wound filler. Another effect of the gauze as wound filler is to ease the pain when applying the pressure due to less contraction in the wound by gauze compare with foam.<sup>139</sup>

Pain and trauma can also be caused by removal of film-based dressings with adhesive skin contact layers that are used to keep NPWT systems in place. Skin stripping may occur because the film can adhere too aggressively to the periwound skin. A solution for this problem may be to choose a soft silicone film instead of an acrylic adhesive-based film.<sup>240</sup>

### Physical discomfort

Patients treated with NPWT also describe other types of physical discomfort besides pain. Being attached to the machine 24/7 seems particularly problematic and bothersome.<sup>566,569</sup> Being forced to carry the device all day also restricts daily living with regards to mobility and physical functioning. Even though it is said that the patients are treated with a so-called mobile device it is of considerable weight that patients describes it as problematic to carry,<sup>570</sup> one patient said:

*'You couldn't even go into the kitchen without carrying it. It is a great burden.'*<sup>569</sup>

The industrial development in recent years has been drawn to smaller and more portable devices. The treatment results in smaller wounds do not seem to differ from the larger devices and the advantage for the patients is in terms of QoL gains when allowing them to be more mobile.<sup>571</sup> There seems to be no difference in pain and patient satisfaction between the devices but major advantages for smaller ones concerning overall activity, sleep and social interactions.<sup>162</sup>

### Sleep

Sleep disturbance during treatment with NPWT



has been described in the literature. Thus the problem exists although it does not seem to be of major severity or of an unmanageable kind. In a study by Upton and Andrews, 56% of patients reported some level of sleep disturbance.<sup>572</sup> The patients rated their problem with sleeping as a mean score of 2.98 on a scale of 0 to 10.<sup>572</sup> A factor contributing to sleep disturbance during treatment is having to sleep in an uncomfortable position due to both the equipment and the fear of causing the machine to shut down.<sup>566,572</sup> In particular, fear of tearing off the draining tube from the dressing was present, which led to some patients being afraid of moving around during sleep and reporting only sleeping on their back.<sup>566</sup>

*'Entangles me in the drainage tube'*<sup>566</sup>

*'Slept badly. Everything feels hopeless.'*<sup>566</sup>

Patients treated with NPWT that experienced some pain relief associated with the treatment did rate their sleep significantly better than those treated with dressings.<sup>9</sup>

## Psychological aspects

### Body image

Treatment with NPWT has been described in the literature as potentially affecting patients' body image and view of themselves. This is probably due to being attached to a machine that makes a constant reminder of them having a wound and for others to notice. There have been described gender differences in this aspect. Appearance seems to be the most problematic for female patients while the sound of the machine was expressed by the males as the most embarrassing. These feelings resulted in the patient living a restricted life.<sup>569</sup>

*'It made me feel very, very uncomfortable and very shy with it. Maybe not shy, but embarrassed ... it was so awkward and ugly.'*<sup>569</sup>

## Stress

Many patients describe treatment with NPWT as being stressful. The most common source of stress mentioned is the organisation of the dressing changes. This is particularly a problem when dressing changes take place in the operating room and the patient has to wait, fast all day and then often is down-prioritised meaning that the dressing change sometimes gets postponed to the next day.<sup>570</sup>

*'So that a ... well ... that part was an inconvenience, to have to wait not knowing if the change of dressing could be done that day ... all of a sudden it could not be done and then you did not know when next a change could be performed ... well you must get a scheduled time for the change of dressing.'*<sup>570</sup>

## Anxiety

Patients treated with NPWT may experience increased levels of anxiety compared with patients being treated with traditional dressings.<sup>236,573</sup> This seems especially present in the group of patients policlinically treated in their home instead of being admitted to hospital.<sup>236</sup> These patients mainly describe their experience with the treatment that they feeling abandoned by the health professionals, coping with the treatment on their own which creates a feeling of being insecure and unsafe. Lack of follow-up and difficulties in knowing where to turn when something goes wrong with the treatment is described by several of the patients. This is something that needs to be addressed by the health-care system in order for the patients to feel that they are being cared for even when being treated outside the hospital or other health-care facilities.<sup>566</sup>

Fear and anxiety regarding malfunction of the machine or that the patients themselves are doing something wrong that will make the treatment

fail is constantly present. They are focussed on the machine which makes it hard for them to relax:

*'I am constantly afraid that the machine will be squeezed and be turned off – check it all the time.'*<sup>566</sup>

By providing the patients with a proper education in the functioning of the machine and informing them what they should do if the alarm of the machine sets off, a confidence and feeling of manageability is created, which reduces the anxiety.<sup>566</sup>

### Staff competence

Since NPWT is a relatively new treatment method the literature shows that health professionals are not always up-to-date and skilled in the performance of the treatment. This also leads to feelings of being insecure and unsafe together with different levels of anxiety and misbelief of health professional in general.<sup>566,569,574</sup> Some patients, however, express an understanding regarding some deficiencies in the competence of the staff since they were aware that the treatment was new, some even expressed an interest in being part of the staff's education.<sup>566</sup>

## Social aspects

### Isolation and stigma

The patient's social life may also be affected during treatment with NPWT. The literature describes how patients can experience it as annoying and embarrassing to be in social settings with the device, that it looks strange and makes a lot of sound:

*'I was glad it was winter because I could cover up with a dark coat ... I was conscious of it ... I didn't want other people to see it.'*<sup>569</sup>

Some patients also describe being concerned that those around them will perceive a bad smell. This can lead to the patients feeling awkward, from

their social life and getting isolated.<sup>574</sup> However, there is research saying that social functioning has been improved during the treatment.<sup>561</sup> It may have to do with these patients receiving a treatment that fits well, no leakage of the dressings and that the device actually dealt with the possible odour making patients feel that they can more easily move out of the social context. Familiarity with and feeling secure about the device can be a key so that patients are not ashamed of it.

### Family and friends

The patient's family plays a major role during the treatment. Patients express being really dependant on the support of their family and friends to feel secure and comfortable during the treatment.<sup>236,566,575</sup> In particular, female patients experience the burden of being dependent on their family for assistance and support, while male patients relied more on health professionals.<sup>569</sup>

*'Had to get (husband) to help me with everything (pause) everything ... very, very incapacitated that I couldn't do it myself.'*<sup>569</sup>

Family members themselves may also describe being affected by the treatment, for example, by being disturbed by the device itself or by the sound of the alarm, and it can interfere with night sleep.<sup>236,566</sup>

## Patient and family caregiver education

NPWT is not an entirely safe treatment without complications. In December 2009, the FDA issued a notification regarding safe use of the treatment and stated that the most severe injuries and deaths associated with NPWT occurred at home or in long-term care facilities.<sup>576</sup> To ensure safe and correct use of NPWT it is important to educate the patients thoroughly. It has been

suggested that lack of education of patients and caregivers may have been a risk factor for complications, especially when being treated at home.<sup>577</sup> It is recommended that the education of patient and family starts at the beginning of treatment and continues throughout the patient's hospitalisation. It is then essential that staff, before discharge, ensure that the patients and family caregivers are prepared to apply the device, are able to monitor the therapy and can respond appropriately to issues that may arise during treatment.<sup>577</sup>

The content of the education has been recommended to contain:

- Written patient instruction regarding safe operation of the device

- Knowledge on how to troubleshoot device alarms
- Competence in application and reinforcement of the dressing
- Knowledge in recognition of signs and symptoms of upcoming complications
- Preparedness to respond to emergency situations.<sup>577</sup>

Knowing where to turn to when something happens while being treated at home is described in the literature as a key factor for the patients to feel confident with the treatment. Unfortunately this seems to be a frequent problem for the patients with a feeling of abandonment and increased levels of anxiety as a result.<sup>566</sup>

# 7. Organisation of NPWT

## Organisation of care

The organisational aspects of NPWT are of particular interest because NPWT might be provided not only as a device/technology, but also as a service, including different purchase or rental models, maintenance systems and cross-sectional coordination.

This chapter deals with the organisation of NPWT in the hospital, primary care and home-care settings. It establishes an overview of the circumstances involved in NPWT organisation in the different settings and provides guidance on which aspects to consider when organising the treatment setup.

## NPWT at different levels

NPWT was initially introduced in hospital care, frequently for acute, traumatic and or post-surgical wounds.<sup>578</sup> This then extended to the treatment of hard-to-heal wounds of other aetiologies in other hospital-based disciplines. Today, NPWT can be applied under different circumstances. It can be used in home care, outpatient or inpatient settings. All three levels come with different requirements and conditions for the clinician, the patient and the carers.

These requirements are widely different when treating a patient in a closed environment such as an inpatient ward with continuous observation or in an outpatient facility or at the patient's home due to the challenges and demands for optimal use of the technology.

## Short- and long-term goals

It has to be recognised that the initial indications for NPWT, so-called short-term goals, which are usually defined in-hospital, are different to the 'long-term' goals, frequently guided by the out-patient treatment plan. The short- and long-term goals must be individually defined for every patient and laid down in their treatment plan.<sup>371</sup>

Short-term goals include:

- Dressing solution
- Management of wound exudate
- Management of wound odour
- Pain management to achieve a reduction in pain
- Prevention of infection.

Long-term goals include:

- Reduction in wound exudate volume
- Intended wound closure through secondary suture or secondary intention healing
- The production of healthy granulation tissue
- A reduction in wound area.

## Reimbursement

One key issue in the use of NPWT as a technique

or service is how it is reimbursed and also whether it is introduced as device only or as a service delivered by the company. This has a substantial impact not only on organisational care, level of care and health economics but also on legal issues.

The reimbursement situation in Europe is complex and varies not only among countries but also from region to region<sup>579</sup> as illustrated by examples in (Appendix 11).

Our analysis shows that in the five countries from which we were able to obtain data (France, Germany, Italy, Spain and UK), two had defined national reimbursement structures for NPWT. The remaining three had no national system in place, leaving it up to regional or hospital budgets to allow for the reimbursement. Also, while the device might not be reimbursed, the treatment might be reimbursed as a dressing change. The reimbursement situation for use of NPWT in the home care setting also seems fragmented. In Italy home care NPWT is not reimbursed; however, exceptions exist in Piedmont, Tuscany and Sicily. In Germany reimbursement is granted on a case-by-case basis, and Spain rarely offers reimbursement. In the UK, NPWT in the home care setting is reimbursed, but not for multi-patient devices and France reimburses the treatment in home care, however, not in community care. (Appendix 11).

The means of delivering NPWT also vary greatly, with all five countries both leasing and purchasing the NPWT devices. In terms of training staff in the

appropriate use of the devices, France, Germany, Italy and Spain rely on companies to deliver the training to staff, whereas in the UK both companies and expert clinicians provide training for staff.

The availability of treatment protocols also varies greatly, from no protocols in Germany to regional protocols in France. In Italy protocols exist in some regions and at the hospital level in other regions. In the UK protocols exist exclusively at the individual hospital level, which is also true in Spain, however, protocols only exist in some instances.

Since the reimbursement and the system for implementing NPWT have a substantial impact not only on the organisation of care, but also on the health economic evaluation and use of NPWT, the challenge to compare NPWT is substantial since there is such a variation among countries and within regions.

## NPWT in different settings

### Hospital

Most European hospitals have typically chosen one particular NPWT system to be used across the hospital. Patients will, therefore, mostly continue to use the same system as the one they were introduced to in the hospital if the treatment was initiated there. NPWTi only makes sense in an inpatient setting, while ciNPWT, which is usually initiated in hospital, is now seeing more outpatient use.

Hospitals have treated patients with NPWT for a long time and provide the best conditions for

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the application, including sterile procedure room, optional anaesthesia, fast availability of analgesics, and trained staff and continuous observation of the patient. In the hospital, patients and/or caretakers can be taught how to use the NPWT device on a regular basis integrated into daily management. NPWT has also been integrated into hospital-based outpatient facilities. On initial application of NPWT, the patient and the dressing should be closely monitored for at least 24 hours to make sure that possible bleeding and other complications are detected as soon as possible and that the necessary steps can be taken.

### Primary care

NPWT has been introduced in outpatient facilities that are not hospital-based, initially for postsurgical wounds, but later for complex and hard-to-heal wounds. How often it is introduced in outpatient facilities is related to the health-care system and the reimbursement system in each country.

For example, in Germany, suitable NPWT devices and dressing materials are chosen and dressing changes are performed by ambulatory care providers, including GPs, surgeons, inpatient and outpatient clinics or by specialised nurses.

Every citizen living in Germany is required to have health insurance. Based on individual income, coverage can be chosen as part of the Statutory or Private Health Insurance schemes (SHI/PHI). In coordination with government health policies, the health insurance companies develop catalogues of minimal service standards, which are then adopted as 'standards of medical care,' which everyone has the right to benefit from.

Hospital care is covered by the standards of medical care and is billed according to the diagnosis related groups (DRG) system. The different medical specialisations have their own cost codes relating to

medical conditions and treatments such as NPWT. In 2016, for example, new DRGs for NPWT in vascular surgery have been introduced.

Outpatient care is also covered by the standards of medical care; however, the full costs of treatment are not covered. The patients are divided into care levels by the medical service of the health insurance companies, which determines the amount per month to cover costs for care services, such as outpatient treatment.

In the UK, for example, the co-ordination of NPWT is often conducted by the tissue viability service, which supports both medical and ward-based nurses in the application and management of NPWT. The tissue viability service also co-ordinates discharge to the community, if continued NPWT is required. Here, both doctors and nurses perform dressing changes. Consumables are reimbursed via the UK Drug Tariff but multi-patient use devices are not. Single patient use NPWT is reimbursed on the UK Drug Tariff.

In the Swedish system, primary care and hospital care are mainly separated in their organisation. Primary care is run by the municipality and hospital care by the county. Private care in both care levels is also available. This can often be a problem when one care provider initiates NPWT and the other takes over the care of the patient in a later stage of treatment. In Sweden, everything is based on the tax system and, frequently, the reimbursement of NPWT as a technology is paid for by the hospital (county) whereas the staff is paid for by the authority.

### Home care

Hospital patients are now discharged earlier than before<sup>580</sup> and as a consequence, more patients (including those with wounds) with a complex pathological condition are being treated in a home care setting.<sup>581</sup>

For the purpose of this document we follow the definition from the 2014 EWMA Document 'Home Care-Wound Care' in which wound-related home care is defined as

*'the care that is provided by health-care professionals and families, also called informal carers, to patients with wounds living at home.'*<sup>19</sup>

The use of NPWT in the home care setting varies greatly among countries, which can be explained by the differences in health-care systems and the reimbursement for the treatment in this setting.

In Germany for example, NPWT is not reimbursed in general, but on a case-by-case decision, depending on the statutory health insurance (SHI) company. The treatment of patients at home in Germany involves coordination between the home care supplier and the SHI to obtain approval and reimbursement for the treatment. The home care supplier applies for a treatment guarantee and organises the device and the equipment required; the supplier facilitates coordination between the attending physician, the nursing service and the patient, if the latter is to receive NPWT in a non-inpatient setting. The home care supplier is not allowed to perform NPWT-related dressing changes, which must be performed by a GP or a surgeon in outpatient clinics. In the meantime, patients are usually not transferred from the inpatient setting until a guarantee for the reimbursement from the SHI has been obtained since most applications for this kind of guarantee have been/are denied. However, home care providers or producers of NPWT devices might cover the costs (in advance) until the guarantee is given.

In the UK, commissioning of wound care services and purchasing contracts for medical devices is locality based and, as a result, equipment for NPWT and the support services necessary for the safe delivery of this form of wound management

can vary greatly.<sup>19</sup> Differences in contracting may mean that community services within a hospital catchment area can use different NPWT systems and have different support structures. This can be a particular problem when patients with complex wounds requiring NPWT are discharged from tertiary referral centres or even when patients are transferred between hospitals.

In Sweden there is advanced intensive care in the home performed by specialised nurses. They can manage NPWT in the patient's home. For home care in a less advanced setting no specialised personnel are required, therefore, the care is also dependent on the health-care personnel's individual competence.

## Basic concepts in the organisation of NPWT treatment

The following provides insights into what is required for the organisation of a NPWT setup that enables safe treatment and secures transfer of knowledge as well as the proper expertise.

It is self-evident that such a setup requires that staff, equipment and permissions are in place, which is why we will focus on the following points.

- Access and service support
- Responsibility
- Organisation of network supporting the patient
- Staff education

## Access and service support

Inventory and single-purchase models

Hospitals have different regulations for access to

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NPWT devices. Some have established a depot with a certain number of devices available. Before using an NPWT device for patient treatment, a simple registration form is filled out and sent to the supplier by fax or email. After use, the device is checked out following the same procedure.

Another option is to order the device directly from the supplier via phone or the internet. However, this method has the drawback that the device cannot be used right away because it has to be delivered first. Hospitals can also purchase NPWT devices from the manufacturer, but if they do, they will also have to manage possible device repairs, if required. The hospital billing system in place in the respective countries provides for the corresponding remuneration for the service provided.

In Sweden different options are available: purchase, lease or rent. It is the choice of the individual health-care facility and often dependent on public procurement in different counties.

The preparation of the device for re-use also follows the hospital's respective approach to the organisation of NPWT. Hospitals maintaining a device depot or owning their own devices prepare the pumps by wipe disinfection after every patient according to the manufacturer's specifications. If the devices are provided by the manufacturer, the manufacturer will take care of regularly checking both software and device.

In an ambulatory setting, patients are either provided with a device directly by the manufacturer or through a home care provider. In this case, the patient, and the attending physician and caretakers definitely need a contact person to help them with possible device malfunctions or complications. Upon termination of NPWT treatment, the device will be picked up and prepared for re-use by the home care supplier or the manufacturer's service staff.

### Leasing model

A third option is leasing the devices from a third party or from the manufacturer. The choice to not sell the machines, but rather to rent them, is a peculiar feature of the NPWT treatment, which puts it more on the side of rehabilitative technologies (i.e. magnetic fields) than dressings and medications.<sup>582</sup> When the NPWT devices are leased, the maintenance responsibility lies with the manufacturer or the third party.

### Free rental model

In this model, the NPWT device is rented and the disposables (the canisters and dressings) are bought. This has been particularly effective in markets where the introduction of the treatment is slow. The free rental business model is becoming more common in Scandinavia and the UK and is well established in southern Europe.

### Disposable devices

Disposable units are bought by the health-care provider and discarded after treatment. It is expected that health-care providers who do not have a leasing contract with the companies but simply buy the devices will lead to an increase in the actual use of NPWT and consequently to a lowering of the tariffs both for the disposable and for the non-disposable devices.<sup>583</sup>

### Managed service

Another way of organising the handling of devices and auxiliary equipment is using a managed service delivering all wound treatment including NPWT.<sup>584</sup> It has been suggested that such a setup might optimally help ensure consistent, high-quality patient care, with sufficient flexibility to meet the needs of individual patients and which also be effective in providing cost-effective treatment across different healthcare settings.

Optimally, the use of a managed service may give the following advantages (adapted from Williams):<sup>584</sup>



- Uses a centralised system for rental, maintenance and purchasing—reduction in rental costs; single maintenance contract paid quarterly and known in advance; reduced waste with all consumables purchased from one supplier
- Produces accurate records, including numbers of patients treated, speciality, wound type, length of treatment and outcome
- Eliminates delay in treatment
- Makes transition from secondary to community care seamless, with more patients being treated at home
- Reduces inappropriate use by limiting authorisation to those who are experienced and knowledgeable in the use of NPWT
- Enables technological advances in products to be implemented effectively (i.e. replacement of older units with newer models)
- Supports integration of all wound treatment options in addition to NPWT

## Service support

How can continuous high-quality treatment be guaranteed?

Whenever a decision is made to continue the patient's treatment in an ambulatory setting, it is important to name one or more contact persons that the patient or the carers and the attending physician can contact if questions or problems arise. Different contact persons should be named for device-related issues and questions concerning the NPWT treatment and dressing.

In Germany, the individual responsible for any questions related to the treatment unit is usually a service employee of the respective company,

whereas the contact person assigned to treatment and dressing questions should have undergone specific NPWT training (typically a specialised nurse or a doctor).

In the UK, specific training in NPWT varies by location. In general, the tissue viability team will provide both theoretical and practical training, often supported by company representatives from the chosen local system provider. This will highlight local guidelines for the use of NPWT. There are no specific UK NPWT qualifications, and nurses would be expected to act within their national code of practice.

In Sweden, the health-care provider has all medical responsibility for the patient's care. Companies, however, must provide technical support, which is contracted in the public procurement. The responsibility for service of the devices is clarified in the public procurement and is either performed by the companies or by the department of medical technicians at the different hospitals.

### Service support with regard to the patient

It is crucial that the patient be informed about which steps to take if there is a problem with the treatment—for example pain, pressure level, leakage—and is able to carry them out. The patient should be informed about the relevant steps at discharge from the hospital preferably with a relative or support person. However, it is still important that the patient be able to get support over the telephone in the case of a malfunction, an alarm or if the seal is breached. This is particularly important when taking the patient population into consideration, which predominantly consists of elderly patients,<sup>19</sup> who might not be very familiar with technology. Therefore, if 24-hour telephone support from the manufacturer and/or the caregiver is not available, a telephone hotline to a section of the prescribing hospital/outpatient clinic manned around the clock is advisable.

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## Responsibility

Responsibilities regarding NPWT also have to be clearly defined for the entire duration of treatment and should be emphasised in the education of staff. In the hospital, this is fairly simple.

Responsibility lies with the attending physician who can then delegate NPWT changes to specially trained staff, if required.

In the non-hospital setting, regardless of whether the patient is to be treated in home care or primary care, responsibilities need to be clearly defined before discharge. In Germany, the main responsibility also lies with the supervising physician who should be trained in NPWT.

In Sweden the overall medical responsibility for the patient's care and for the NPWT treatment is with the physician who has initiated the treatment, even when the dressing changes are done by primary care. If the district physician has initiated the treatment the responsibility is with primary care.

## Education and providing a network supporting the patient

If therapy is to be continued in an ambulatory setting, a suitable network for ideal patient care in that setting should be drawn up before initiating NPWT in the hospital. In Germany, so-called wound networks consisting of members working in all three settings have been established in several regions. These organisations can facilitate a well-managed transition of the patient from the inpatient to the ambulatory setting.

This approach requires a case manager who has an overview of the current status of treatment and, if necessary, can organise a visit to the attending physician. The case manager is aware of the duration of treatment and, if required, can challenge the remaining duration of NPWT. While, useful, wound networks with case managers are far from being established in all regions of Germany.

One of the basic prerequisites for a well-working patient care network is good communication among all parties involved. That is the only way that continuous patient treatment be guaranteed.

In the UK, there is no specific patient or carer network for the support of patients receiving NPWT either in a hospital or community setting. It is recommended that patients and/or carers should, when receiving NPWT in a home care situation, be provided with appropriate supporting literature and basic training in the management of the dressing and the equipment.

In Sweden the patients should get information on whom to turn to during treatment at home. This has, however, been a major problem for patients with the result they often feel abandoned by health professionals and left to manage the treatment on their own.<sup>566</sup> In Sweden there is no formal requirement that personnel should have specialised education in wound care before initiating or treating patients with NPWT. The knowledge and competence of health professionals may therefore vary and are often dependent on the individual's experience and interest. It is, however, only physicians who have the right to prescribe the treatment, but it is most often managed by nurses.

## Minimum requirements for staff education

To ensure that scientific evidence is carried into daily clinical practice, there is a need for a knowledge transfer model that articulates an educational plan for the various levels of professional development.<sup>585</sup> The staff education should highlight the challenges and potential solutions to integrate NPWT into a seamless continuum of care including a community-based patient care model. The education should include the basic concepts of tissue debridement, infection/inflammation control and moisture balance. Staff should also be trained

to understand the basic principles of pump and dressings and to be able to take appropriate measures if necessary.

### Questions to be considered before initiating therapy

Regardless of whether the treatment is to take place in the home care, primary care or hospital setting, the following questions should be answered before initiating therapy:<sup>371,486</sup>

- Is it possible to effectively debride the wound bed and wound before applying NPWT?
- Can NPWT be used based on the results of wound assessment?
- Can or will the patient's symptoms be improved with NPWT?
- Are there contraindications to NPWT (Chapter 5)?
- What are the treatment goals to be achieved through NPWT—preparation for secondary suture, wound preparation, exudate management?
- After discharge, who will perform dressing changes—the hospital, home care, primary care?
- Who supplies dressing kits and devices?
- What is the intended duration of treatment?
- Does the patient back the decision to perform NPWT? If so, what are the prerequisites?
- Does the patient consent to the treatment and is adherence expected?
- Is communication between parties secured and well described with each other: GP/surgeon, attending nursing service, home care supplier and hospital?

The high drop-out rates in the literature<sup>163,578</sup> suggest that the adherence and outcome of the treatment is more related to the staff competence, choice of patient and wound, than to the technology itself. This underlines the need for a coherent academic training programme for staff working with NPWT.

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# 8. Documentation, communication and patient safety from the medico-legal perspective

NPWT is an increasingly common form of wound management applied to patients with a variety of complex wounds. These patients often move through the care system, receiving care from multiple agencies working across service boundaries. This development raises an increased awareness of the need for documentation, communication and patient safety, particularly from the medico-legal perspective.

## Implications of cross-sectional NPWT

A substantial challenge for out-of-hospital treatment with NPWT is the patient population (comorbidity, capacity for adherence) as well as the experience and skill of the staff, particularly in an environment without continuous observation of the patient. As a consequence, the cross-sectional use has implications for both the delivery and acceptance of NPWT in an out-of-hospital facility (primary care, out-patient facility, patient's home). Increasing use of NPWT has seen a progressive move to deliver therapy in a home care situation. Dowsett et al.<sup>278</sup> have

demonstrated both the significant cost benefits and improved outcomes that such a shift in care delivery location can bring. Moffat et al.<sup>586</sup> highlighted the potential emotional impact that home NPWT may have on both the individual and the family but found an overall benefit to home NPWT provided that there was thorough discharge planning, good service co-ordination and communication. When discussing the impact of medical support in the home Teot comments :

*'The relatively low interest of wounds for many doctors can create problems in term of medico-legal consequences and may lead to over cautiousness in terms of decision making.'*<sup>587</sup>

To overcome the barriers to introducing NPWT in out-patient facilities, it is essential that the rationale for initiating NPWT as well as the responsibility for the treatment be clearly defined for the entire duration of treatment. Thus, introduction and acceptance of NPWT in those settings requires careful discharge planning with 'transitional' protocols and support in place if care is to be delivered safely, cost-effectively and without interrupting therapy between care settings.

Guy and Grothier<sup>370</sup> have developed a suggested community NPWT pathway, which supports the patient and the care team through the discharge process. Similar locality-based care pathways should be developed to facilitate smooth care transition.<sup>584</sup>

These protocols need to address:

- Communication between care teams and organisations with:
  - Agreed equipment strategy and documentation
  - Co-ordinated ordering of pump systems and consumables
  - Ongoing follow-up arrangements
- Contingency plan for equipment shortages and failures
  - Additional equipment rental agreements and funding streams
- Out-of-area transfers
  - Continuity of care when different or no NPWT systems are supported/funded
- Equipment returns and decontamination
- Clinical incidents, training, monitoring and review procedures
  - Learning across organisations and boundaries.

Protocols need to address not only issues related to patients, in a care facility or their own home but also how patients will be seen and assessed in out-patients or a general practice surgery and how NPWT will be managed during diagnostic

tests such as magnetic resonance imaging, when equipment such as the pump has to be disconnected for a variable period of time. Most manufacturers suggest that therapy can be discontinued for up to two hours before a dressing must be replaced.

## Off-label use

Although the basic principles are the same, the success of NPWT has resulted in an explosion of devices, wound fillers and drainage kits with different therapy characteristics and operating instructions. More than 25 FDA Class II approved NPWT devices were available commercially in 2014. Devices can now be mains, battery or mechanical powered. They have a variety of drainage tubes and offer a range of collection system volumes designed to accommodate different wound types, sizes, positions and exudate levels. In addition, the wound contact layer may be gauze or a variety of foams. Each manufacturer has designed components as part of an integrated and regulatory framework-approved system and only within each system can negative pressure profile and wound interphase pressure be relied upon. This means that component parts from different manufacturers should not be built into a self-assembled NPWT system and that the disposables are not interchangeable. To use unmatched components in such a way represents off-licence usage. Complications resulting from such actions are, therefore, the sole responsibility of the individual and institution/provider and not of the manufacturer.

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## Contractual terms and agreements

Health professionals need also to be aware of the local contractual arrangement, and terms and conditions established with the chosen provider of NPWT systems and components. This will vary between suppliers and may differ between purchased and leased items. Contracts should specify arrangement for equipment maintenance, cleaning and sterilisation schedules and identify lines of responsibility both during and between patient care episodes.

## Patient safety issues

Reports regarding adverse reactions in the treatment of patient with NPWT indicate the need for clear instruction to the staff as well as the patient, with regards to patient safety issues. This is illustrated by the Pennsylvania Patient Safety Reporting System<sup>577</sup> which highlighted a number of patient safety issues in relation to NPWT, although some of these issues related to general poor wound assessment and documentation. It found:

- Inadequate or lacking assessment (5%)
- Delayed or incorrect application (21%)
- Inadequate monitoring and ongoing assessment (47%)
- Discharge issues (7%)  
—carer/patient education
- Other events (20%).

Martindell,<sup>577</sup> in her review of the Pennsylvania Patient Safety report, comments on the vast number of NPWT systems available and stated that a nurse caring for a patient using NPWT must be familiar with the manufacturer's instructions.

Notably, indications for use and application methods are not the same for all devices.

Treating complex wounds, particularly with high-tech strategies, carries with it the risk of treatment complications. Cases have been reported that highlight the danger of NPWT close to exposed viscera and blood vessels. In an FDA preliminary public health notification,<sup>588</sup> bleeding was identified as the most serious complication occurring in 6 deaths and in 77 injuries. Following these and other NPWT treatment complications, the FDA has put forward a number of recommendations and precautions in relation to this form of therapy. These can be summarised as:

- Careful patient selection, especially in relation to wound type
- Selection of the appropriate care setting for high-risk patients
- Wound-care and appliance-specific considerations
- Documentation and communication
- Training of health professionals, patients and carers.

## Patient safety checklist for out-patient NPWT

An area that is considered critical when NPWT is used in an out-patient situation is training for patients and caregivers. Patients and carers should know how to:

- Safely operate device  
—Provide device-specific information
- Respond to alarms

- Deal with seal leaks
- Change dressing or downgrade to a ‘normal’ dressing
  - Ensure dressing material is available on site
- Recognise complications
  - Bleeding
- Respond to emergencies
  - Stop NPWT
  - Apply direct pressure
  - Activate emergency services
- Contact support

## Communication

One common theme throughout these recommendations is that communication both among health professionals and between health professionals and patient must be robust if NPWT is to be delivered safely and effectively. Documentation serves a number of purposes by:<sup>589,590</sup>

- Promoting better communication and sharing of information among members of the multi-professional health-care team
- Making continuity of care easier
- Showing how decisions related to patient care were made
- Providing documentary evidence of services delivered
- Supporting:
  - Delivery of services
  - Effective clinical judgments and decisions
  - Patient care and communications
  - Clinical audit, research, allocation of resources and performance planning

- Helps it to:
  - improve accountability
  - identify risks, enabling early detection of complications
  - address complaints or legal processes.

## Documentation

A number of authors have highlighted failings in nursing and medical records, including records associated with wound care and PU management.<sup>591–593</sup> Medical and nursing notes form part of a legal record and can be an important piece of evidence. As such, notes must be thorough, accurate, factual, objective, legible and free from abbreviations unless these are defined. They should also be contemporaneous and truthful, signed, timed and dated. When detailing wounds, particularly cavity wounds, hand-written notes can usefully be supplemented with orientated ‘scaled’ diagrams, maps and photographs.<sup>594</sup> Accurate and detailed cavity wound documentation is particularly important, if the danger of retained dressing material is to be avoided. Notes should record:

- The wound packing material(s)
  - Material type
  - Size
  - Number
  - Location
- If used, number and type of wound bed contact layers.

The written description should be combined with a diagram illustrating the relationship of the packing material to the wound, recording where packing extends into undermined areas and therefore may not be visible at the next dressing change. Packing material and wound filler should be counted in and out and action should be taken if any discrepancy is noted. There have

been reports of adverse events related to materials and wound fillers.<sup>595,596</sup>

## Legal and litigation issues

Legal proceedings involving NPWT are increasing.<sup>19</sup> Risk reduction requires understanding contraindications for use and early recognition of potential complications of NPWT and, as such, exposes the inexperienced user to greater risk.<sup>19</sup>

Legal and litigation issues in relation to NPWT can be divided into the following areas:

- Retained dressing material
- Failure to respond to alarms
- Failure to follow manufacturer guidelines
  - Pressure settings/off suction duration
  - Dressing intervals
- Inappropriate case selection/assessment
  - Failure to respond to bleeding

- Training and staff/care-system response
- Communication and documentation
- Skin/pressure damage related to tubing and poor dressing technique.

The complex nature of some wounds may mean that care is experimental (e.g. vascular surgery and groin infections) and the use of NPWT in such cases may extend outside of the manufacturer guidelines and breach rules on contraindications to therapy. In such cases a full explanation of the care decisions must be recorded, including recognition of off-licence usage and the patient's permission for such care. Care must be closely monitored and only undertaken by health professionals experienced in the use of NPWT.

In summary, the use of NPWT is not only an issue with regard to technology and wound treatment but also represents a fundamental change in terms of the legal aspects and patient safety issues in the high-tech treatment of wounds.



# 9. Health economics

The introduction of NPWT represents an innovation not only from a clinical perspective, but also with regard to health economics, organisation resource use. This novel form of wound management is differentiated from the existing approaches by increased demands for a clear definition and interpretation of resource use and cost-effectiveness. This applies both to the management of closed incisions, complex, and in hard-to-heal wounds.<sup>597-599</sup> To understand the potential impact of NPWT, there is a need to recognise the challenges in the analysis of resource use and economic cost in the treatment of wounds.<sup>15</sup>

A major problem in the analysis of the cost of disease states is that comparisons of cost analyses are compounded by variations in care protocols and the economic status of different countries, for example, variations in rates of pay for health-care staff and reimbursement.

There is an increasing demand for quality outcome data to support the economic decision-making process, which turns our attention to resource use efficiency and assessment of consequence rather than simplistic cost arguments, particularly in post surgical wounds, PUs, lower LUs and DFUs.<sup>15</sup> The current models of care are often fragmented in their delivery and reflect exclusively on intervention versus cost over time.

Successful projects are often associated with a broader perspective including not only the costs of dressings and material but also costs of staff, frequency

of dressing changes, total time to healing and QoL.<sup>15</sup> A correct wound diagnosis is a prerequisite for accurate and successful care, the use of more effective dressings and wound care material, choice of dressings suitable to type of ulcer and diagnosis, measures to improve healing and avoid recurrent ulcers, and shortening of total time to healing.<sup>15-17</sup>

## Organisation of care

When dealing with health economic analyses and resource use in complex wounds, with regards to NPWT technology, it is essential to look at its impact on organisation of care both in-hospital and when used across sectors.

It is less common to study and evaluate organisation of wound care or management systems but these studies can provide important and useful information to improve the outcome of wound care. It is also important to be aware of costs associated with non-optimal management of complex wounds, particularly in cases with cross sectional care. The economic impact of organisation of care and the consequences of the lack of coordination between various disciplines and levels of care, as has been illustrated in reports with regards to management of DFUs.<sup>600-603</sup>

These findings have been confirmed in various countries and health-care systems globally indicating the danger with regard to fragmented care and lack of communication between care-givers.<sup>604-614</sup>

Many health economic studies in hard-to-heal

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wounds have been focused on reduction in in-hospital stay and treatment at hospital-based specialist clinics. However, a substantial number of resources are used in outpatient facilities in primary care/home care.<sup>19</sup> The finding that home health-care accounts for a significant proportion of the resources spent in the treatment of individuals with hard-to-heal wounds indicates that the trend towards high-quality care based in outpatient clinics and home care is and will be of major importance. A substantial number of studies indicate the importance of organisation in wound care, as well as coordination of treatment strategies to achieve an optimal care with regard to both outcome and cost.

## Factors related to healing of hard-to-heal wounds

NPWT is introduced as a technique or a service in the treatment of wounds more related to the condition of the wounds than to the aetiology of the wound. Currently the majority of studies in wound management are performed based on the aetiology of the wound. The challenge in all these studies and particularly in NPWT is to recognise and control for heterogeneity in individual states and confounding factors as well as variation in type, site and condition of wounds. The distinctive feature of an economic approach to the evaluation of health-care interventions is that it involves explicit consideration of both the costs and the outcomes or consequences of an intervention. As a consequence a health economic analysis relies heavily on adequate information regarding comorbidity and basic standard of care as well as the natural outcome. Today there is a substantial limitation regarding large cohort studies following patients to healing and identifying factors related to outcome and resource use.

## Technologies in the treatment of wounds

When NPWT was introduced, health economics analyses were focused on in-hospital treatment. However, when used across sectors, in outpatient facilities, primary care and home care, the challenge was to understand the impact of NPWT as a device or a service adapted on a broader view, particularly, since NPWT was initially considered expensive, demanding and time consuming, Health economics reports concerning dressings were evaluated to determine if they resulted in less frequent dressing changes or in faster healing.<sup>15,615,616</sup>

When assessing use of resources, it is important not to focus on individual items such as dressings or procedures but to adopt a broader view of total resource use. Few studies in wound care provide a full cost-effectiveness analysis.<sup>15,616</sup> Most studies focus on clinical outcomes only and include analysis of the estimated direct medical costs of treating wounds but not indirect costs relating to loss of productivity, individual patients' and family costs and loss of QoL.<sup>15-17</sup>

Costing is a two-stage process. The first stage is to measure the quantities of resources used,<sup>15,17</sup> and the second is to value those resources. In an analysis of RCTs in hard-to-heal ulcers published after 2003<sup>15</sup> it was found that cost and resource use was used as an endpoint in 4.5% (of the total number of endpoints registered). This could be in the shape of economic costs related to healing, institutional costs, cost per week, resources used, number of dressing changes, cost savings or costs per patient per year. Most of these cases were primarily descriptive and there were concerns regarding items included, the perspective of study and lack of distinction between resources used, costs and charges.<sup>15,19,605,609-611,614,617-619</sup>

## Comparing treatment interventions

To get approval to introduce a new treatment strategy, it will be mandatory to present evidence including health economics, which compares the existing standard treatment with a new treatment alternative, particularly in the case of a technology like NPWT. For this reason there is an increasing need for valid cost and resource-use studies. At the moment there are few high-quality studies with regard to wound management and there is confusion as to how these studies should be performed, especially with regard to endpoints and resource use.<sup>15</sup> There is a limited number of health economic studies on NPWT (appendix 12 and 13), and particularly with regard to cost-effectiveness.

### Cost-effectiveness studies

Cost-effective analyses are commonly used, sometimes misused in referring to all types of economic evaluation in health care. A few cost-effectiveness analyses or full economic evaluations of treatment alternatives for hard-to-heal and post surgical wounds have been performed according to those methodological demands.<sup>620,621</sup> Many published reports supply data without simultaneous consideration of outcome or consequences. These studies can primarily be interpreted as some sort of cost of illness or cost identification analyses and can provide valuable information for policy makers or supply data for planning and execution of future economic evaluations.

Cost-effectiveness studies incorporates both cost and effect. The advantage of these analyses is they consider the possibility of improved outcomes in exchange for the use of more resources. Cost-benefit analyses includes a decision about whether the cost is worth the benefit by measuring in monetary terms.<sup>15</sup> Many studies contain different

resources included in addition to cost items which further complicate comparisons.<sup>15,602,603,616</sup>

### Modelling studies

An alternative to evaluations based on results from cohort studies and RCTs is to perform modelling studies with the application of data from different sources. There are some modelling studies performed with regards to NPWT, particularly in the area of DFUs.<sup>164,622–629</sup> This type of study does not differ from above mentioned health economic analyses regarding the demand for costs being considered in relation to outcome. Modelling is often an option when the perspective of an intervention covers a long period of time.<sup>611,612,620</sup>

### Controversies regarding health economic evaluations

The number of health economic studies of the treatment of wounds is limited and most frequently based on non-comparative case studies or clinical trials comparing a specific treatment or strategy for a specific period of time.<sup>15–17,602,616</sup> The same pattern can be seen with regard to NPWT (appendix 12 and 13). From an economic perspective these studies create a substantial challenge since they actually only measure the resources used in a clinical trial based on a specific premeditated clinical protocol. One concern is external validity—how much daily practice differs from the environment in a trial setting and if all patients are followed to a specific end point or just for a short observation period.

One challenge regarding NPWT is to evaluate the cost of the technology or service from a broader perspective. Product costs frequently have been considered to be synonymous with the cost of care.<sup>15</sup> However, the purchase price of dressings or technologies rarely forms a significant fraction of the actual cost of care. These costs are often negligible in comparison with other factors such

as costs associated with frequency of dressing changes, nursing time, effectiveness in relation to time-to-heal, quality of healing (avoidance of wound recurrence), ability to return to paid employment and the cost of the care setting. Cost-cutting exercises that focus on the use of less costly dressings or technologies might, for example, result in higher overall costs if dressing change frequency is increased (necessitating increased nursing time) and time-to-heal is extended. In some studies evaluating NPWT, in out-patient settings, the finding is that you achieve a reduction in the use of staff due to less frequent dressing changes (appendix 12 and 13).

### Health economics and reimbursement with regard to wounds

The health economic analyses with regards to wound treatment and various technologies are very sensitive for the influence of reimbursement and from which perspective the analysis is done, i.e. payers perspective or societal perspective. The influence of reimbursement has been discussed in chapter 7 on the organisation of care.

## Wounds treated with NPWT

### Cost-effectiveness

Determining the cost-effectiveness of NPWT is a challenging task, particularly when considering the treatment's impact on wound management, organisation, competence of staff and reimbursement. This complexity of influencing factors complicates the decision on which costs to include in the calculation and how to perform cost-effectiveness analysis. Should, for example, cost be derived from cost per day, cost per treatment or cost per wound treated. Furthermore, if the treatment is provided via rented devices, should the calculation be based on the service package adapted to the number of devices rented or the cost of a single machine per treatment? The same applies for the investigation

of the effectiveness of the treatment which widely depends on which outcomes are adopted; wound closure, wound bed prepared for grafting or amputations avoided.<sup>630,631</sup>

### Components of costs

Costs are also difficult to determine because their composition vary. The calculation can be determined by service costs, but could also include staff hours, materials, dressing changes as well as in-hospital days and potential adverse events.<sup>632,633</sup>

When investigating the health economic aspects of NPWT it should be taken into account that the treatment marks a major shift in terms of patient- and wound care, particularly for extensive complex acute wounds, postsurgical wounds and chronic wounds for both in- and out-hospital patients. It has changed the way caregivers treat wounds and introduced new variables in the system. Where conventional wound management is centred around repetitive and frequent dressing changes, NPWT demands less frequent but more complex and time consuming dressing changes. Hence, by introducing NPWT, work and resources are shifted from one activity to another rather than decreasing the overall time consumption.<sup>634</sup>

In this section we focus on some of the most relevant aspects related to resource use, economic cost and cost-effectiveness of NPWT by using the available evidence to give the readers a systematic view of the health economic aspect of this therapy

## Evaluation of comparative and non-comparative studies: resource use and economic cost

In a systematic search (PubMed, CINAHL, Scopus, Web of Science and manually) 270 studies and reviews were identified and abstracts obtained

with regard to health economics and resource use in the treatment of wounds with NPWT. Based on an initial evaluation, 176 of these papers were excluded, and following a detailed analysis another 15 papers were excluded (no original health economic/cost data provided, results not reported properly/did not appear which costs were associated specifically with NPWT treatment, lack of the relevant parameters) (appendix 14).

Included in the evaluation were 48 studies, 39 were comparative and 9 non-comparative (appendix 12; 39 studies,<sup>2,164,250,280,284,395,422,446,489,622-629,632,635-655</sup> and appendix 13; 9 studies).<sup>11,20,634,656-661</sup> The comparative studies include 14 RCTs,<sup>250,280,284,395,422,446,635,636,639,641-643,650,652</sup> 12 cohort studies,<sup>632,637,638,640,644,646,648,649,651,653-655</sup> 4 case studies,<sup>2,489,645,647</sup> and 9 modelling studies.<sup>164,622-629</sup> The number of patients in the RCTs were 16–324, in the cohort 10–13,<sup>556</sup> (one claims data from a database), in the case studies 7–20, in the modelling studies 82–1721. The comparative studies included surgical/postsurgical wounds (n=8), diabetes related wounds (n=8), acute or traumatic wounds (n=5) chronic ulcers/LUs/PUs (n=9), various/mixed/miscellaneous ulcers (n=8). There were three comparative studies which evaluated various NPWT techniques, the remaining compared with various conventional or standard treatments (dressings).

### Complex surgical, postsurgical wounds and acute or traumatic wounds

In the eight comparative studies of patients with surgical or postsurgical wounds treated with NPWT four were favourable with regard to resource use or economic cost, two were neutral and two were unfavourable.

In the five studies of patients with acute or traumatic wounds one was in favour for NPWT, one was neutral and three were negative with regard to resources spent or economic cost compared with other treatment strategies.

The most common results from studies in favour of NPWT is that it aids a faster healing rate than other wound healing therapies, and that the shorter healing time brings the overall costs down to a cost-effective level even though NPWT is typically a more expensive measured per dressing. Regarding complex postsurgical or extensive acute wounds a reduction of in hospital stay is frequently reported

Other studies report that the timing of the treatment matters, so that early treatment is more cost-effective than late, that non-commercial NPWT-systems prove to be cost-effective compared with commercial ones, and that mobile NPWT-devices for use in home care settings seems to be a cost-effective (and patient convenient) solution.

### NPWT in chronic wounds

In nine studies including chronic ulcers/LUs/PUs four were in favour of NPWT, four were neutral and one in favour of a comparative treatment with regard to resources spent or economic cost. In addition the studies of hard-to-heal or non-healing ulcers of various aetiologies four were in favour and four were considered cost neutral with regard to NPWT versus a comparative treatment (appendices 12,13). The following examples address findings from our analysis addressing chronic wounds.

Augustin and Zschocke reported a higher level of QoL and satisfaction among people treated with NPWT in a study comparing two different forms of application in a cohort of 176 patients.<sup>662</sup> They emphasised how this finding would be of importance when the decision of which treatment to choose for the patients, would be made according to the principle:

*'no decision about me without me.'*<sup>662</sup>

Braakenburg et al. comparing NPWT with dressings in a RCT demonstrated how NPWT was

associated with better efficacy parameters also with a better cost/effectiveness ratio, mainly due to the reduction in the times of application of the devices and the less frequent changes that allowed a sparing of the resources use per patient.<sup>663</sup>

Vuerstaek et al. in a prospective RCT comparing NPWT and dressings in chronic wounds, reported faster healing in the NPWT group.<sup>664</sup> Furthermore, a more favourable economic profile due to faster healing, which was associated with a reduced length of hospitalisation and a global reduction in costs.<sup>664</sup>

Abotts et al. and Dowsett et al. both concluded, after prospective studies, that the home use of NPWT significantly reduced the costs by reducing the hospital related treatment.<sup>278,574</sup> Since patients were earlier and more frequently discharged from hospital and managed on a outpatient basis, there was a considerable reduction of resources consumption.<sup>278,574</sup>

The data for ulcerations, PUs, VLUs and postsurgical wounds, are still sparse or, when available, ambiguous.<sup>640,646,650</sup> However, a review by Searle and Milne concluded that there is enough evidence showing the cost-effectiveness of NPWT compared with standard treatment.<sup>634</sup>

The main reason data is unavailable is because good-quality prospective studies in this field have not been conducted. Dumville et al. came to the same conclusions in three Cochrane reviews on LUs, PUs and surgical wounds left to heal by secondary intent. No evidence is available for addressing cost-effectiveness of NPWT in each of these indications.<sup>12,13,421</sup>

### NPWT in diabetic foot ulcers

DFU was probably the first field using NPWT in which data on cost-effectiveness were available, coming both from retrospective and prospective trials.<sup>665</sup> In eight studies of DFUs in individuals

with diabetes, six are in favour of NPWT, one was considered neutral and one in favour of an alternative treatment with regard to resource use and or economic cost. It has to be recognised that the studies with the most impressive outcome with regard to resources spent and economic cost were US studies including foot ulcers following surgery (revision/resection) or minor amputations.<sup>9,10</sup>

Apelqvist et al. in a prospective RCT on NPWT versus moist dressings in post-amputation wounds, demonstrated superiority of NPWT when number of procedures, dressing changes and outpatient visits were considered.<sup>3</sup> Despite not observing any difference in number of admissions or length of stay between the groups; they demonstrated a significant reduction in resources and costs in the NPWT group, considering both the cost per treatment and the cost to achieve healing.<sup>3</sup> Similar results were produced by Driver and Blume in a retrospective analysis of patients enrolled in a RCT comparing NPWT with moist dressings over a 12-week treatment course.<sup>642</sup> Here, NPWT proved to be more cost-effective than standard care, mainly due to a reduction in health-care resources. The authors calculated that the costs for closing 1 cm<sup>2</sup> hard-to-heal-wound was 100 % higher in standard care than when treated with NPWT.<sup>642</sup>

Despite these and other studies, that indicate the value of NPWT with regard to resource use and cost in complex wounds in individuals with diabetes, there is a reluctance in accepting NPWT as a cost-effective therapy for DFU, which might be explained by NPWT in comparison with the existing standards, was considered costly and not so user-friendly.<sup>666,667</sup> This is probably one reason why NPWT in the literature is still not considered to have demonstrated enough evidence to be considered a valuable strategy in managing DFUs.<sup>14,21,668</sup>

## General findings

The number of indications and clinical protocols for NPWT challenges the defining criteria by which to evaluate NPWT from an economical point of view. However, there were transversal items used in most of the studies which included integration of healing rates and healing times with cost per day of treatment, days of admission reduced by transfer to community care, the avoided surgical revisions, recurrences, readmissions and infections deducted from the number of events.<sup>669</sup>

This shift from efficacy to resource use and economic cost to achieve an outcome was prompted by the need to demonstrate superiority of the novel treatment, which in comparison with the existing standards was considered costly and not as user-friendly.<sup>666,667</sup>

The economy of NPWT is still debated, since little high-quality data are available. Due to this gap, the reviews and guidelines do not give solid assessments on the cost-effectiveness. Despite a certain level of agreement between resource reduction and the reduction of in hospital stay, staff hours per treatment are expected to be stable irrespectively of these circumstances.

It has to be recognised that the impact on resource use and economic cost with regard to the use and indications of NPWT in patients with surgical wounds and chronic wounds is more complex than just healing rate and time-to-heal. NPWT impacts on health-care organisations and calls for relevant adaptation in terms of competence of staff, in- and out patient organisation and updated reimbursement system and illustrates the transformation in wound care from passive topical treatment to an era of complex treatment modalities.

## Methodological considerations

There is a remarkable variation in the parameters

that are included in the evaluations, even within the category of 'direct costs'. Widely used are length of hospital stay, cost of labour, cost of materials and total costs. But these are far from represented in every evaluation, and it is seldom clearly stated exactly what each type of cost measurement contains, total cost being the most comprehensive and thus problematic to compare without clear specifications. Various endpoints are used or not defined. Some studies conclude on niche parameters such as antibiotic usage, charges to facilities or material rental fees, while others evaluate in far less detail. Parameters in the category of 'intangible costs' such as pain is mostly seen in the RCTs.

The consequence of these findings are that the results from most of these studies has to be interpreted with caution and put in the perspective from which environment, type of patient/ulcer (study population), health-care and reimbursement system they have been performed.

### A paradigm shift in NPWT: inpatient to outpatient care, a service to a product

There is a shift in the application of NPWT from an in-hospital services, provided by highly specialised units, particularly in postsurgical wounds to an outpatient management strategy, which, after the prescription that is mainly done during hospital admission, is carried on by visiting nurses on outpatient basis.<sup>650,670</sup> This shift toward an increasing ambulatory use of NPWT is closely connected to the introduction of disposable devices.<sup>164</sup> This has led to a considerable reduction of costs per treatment, which can now be integrated in different phases of the complex therapeutic strategy of the patients, as a complement to other options such as hyperbaric oxygen therapy, surgery, dressings, medical therapy, grafting.<sup>671,672</sup>

It is suggested that this could increase the use of NPWT and the number of its indications and

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applications, reducing constraints of the service and costs to an extent that could be affordable also for low-complexity chronic wounds, not only for the major pathologies.<sup>278,585</sup> In this scenario, cost/

effectiveness evaluations done so far should be integrated with the new information coming from the developments in the management of acute and surgical wounds as well as chronic wounds.<sup>139</sup>



# 10. Future perspectives

In this final chapter of the document we aim to reflect on where technological developments within NPWT seem to be going and continue to discuss some of the main clinical and organisational aspects that can be expected to influence future spread and uptake of NPWT in clinical practice.

## Technological developments

Technological advances within NPWT are currently seen to be heading in several directions.

### Hospital-based system with increased sophistication

Hospital-based devices are developing in the direction of increased sophistication and delivery of adjunct therapies such as saline irrigation/instillation, either intermittently or continuously with NPWT.<sup>43,495,504,673</sup> The benefits of powerful antimicrobial solutions for wounds with a high bioburden are under intense investigation.<sup>462,474,497</sup> In another related direction, the delivery of alternative active substances such as insulin<sup>508</sup> or doxycycline<sup>506</sup> are being investigated, as yet on a non-commercial (off-label-use) basis.

### Simplified single use devices

There is a substantial development, almost as it were in the opposite direction, in the use of simplified single-use NPWT devices.<sup>163,382,403,530,674–676</sup> This development, which includes both electrically-powered and mechanically-powered devices, recognises the benefits of the accessibility of NPWT 'off-the-shelf' and with a lower cost base.

This permits the widespread adoption of single-use devices in the emerging prophylactic use of NPWT to reduce complications, such as dehiscence or infection, when used over closed surgical incisions.<sup>383,677</sup> In addition, single-use devices do not restrict patient mobility as they are small in dimension and self-contained.

### New material for wound fillers

The properties of the wound dressing or wound interface determine most of the effects of NPWT on the wound bed.

The currently used wound fillers are commonly foam or gauze. The interaction between the wound dressing and the wound bed has been described in detail for foam and gauze.<sup>57</sup> Both these wound fillers have a mechanical effect on the wound. The tissue surface is stimulated by the structure of the wound dressing. This will trigger the cells to divide to rebuild and strengthen the tissue. The amount and character of granulation tissue formed may differ between the two dressings. The use of foam as a wound interface in NPWT produces thick, hypertrophic granulation tissue. Gauze under NPWT results in less thick but dense granulation tissue.<sup>57,678</sup>

There are other difference in properties between foam and gauze in that the porous structure of foam allows greater volume reduction under pressure. The effect on the wound is also dependent on the size of the foam or amount of gauze filler, for example, a higher tissue pressure is achieved by a small foam filler compared with a large foam filler.<sup>184</sup>

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In the instances when the wound bed is covered by a wound contact layer, the micro-deformational effect is lessened compared with when the foam or gauze is in direct contact with the wound bed, which will affect granulation tissue formation.

A novel wound filler is a bacteria- and fungus-binding mesh. It produces a significant amount of granulation tissue in the wound bed, more than with gauze, without the problems of ingrowth, as is the case with foam.<sup>179,186</sup> Like gauze, bacteria- and fungus-binding mesh has the advantage of being easy to apply to irregular and deep pocket wounds. Efficient wound fluid removal in combination with its pathogen binding properties makes hydrophobic mesh an interesting alternative wound filler in NPWT.<sup>179,186</sup>

There are vast possibilities for further development of novel wound fillers and this will presumably focus on tailoring the compressibility of the wound filler for altering the effect on wound contraction (or macro-deformation). Attempts have been made to alter the pore sizes in the wound filler. There is also an opportunity for development of the surface structure of the wound filler in order to tailor the micro-deformational effect on the wound bed, to hinder ingrowth in the wound filler or even to make the dressing material resorbable.

### Systems with integrated sensors for long-distance monitoring

Next generation NPWT are devices are thought to be incorporating sensors with the ability to continuously measure selected wound parameters and a form of basic remote communication capabilities. The use of different types of wound sensors combined with technologies that are able to analyse and process this data will make it possible to collect, record and analyse data streams quickly and accurately over time. Hence, be able to identify the early signs of infections, specific bacteria and indicate the direction of personalised

therapy.<sup>679,680</sup> The use of sensors and remote communication facilities hold potential benefits and it is stated to be able to increase the quality of care delivered, reduce costs and improve access to specialised care for people living in remote places.

The quality of care is improved by the availability of prompt and detailed clinical outcome data that will allow the health-care provider to define an optimal and timely treatment pathway and to possibly accelerate the healing of the patient.

Savings are to be achieved through the possibility of taking preventive actions and avoiding acute and severe complications due to delays in diagnosis.

Better access to care is achieved for people living in remote areas since this will allow for specialist care at a distance. The remote monitoring function could also lead to better adherence in the community care setting to the treatment prescribed since deviances can be promptly discovered and addressed. Another positive effect of these distant linkages between community carers and specialist care is the learning opportunity for community nurses achieved through ongoing feed-back from in-hospital specialists.

The ability to measure and collect continuous data on the development of different wound parameters also holds potential in terms of collecting BIG data for research due to the possibility of pooling individual outcome data.

This type of device holds great potential but there are still some essential development challenges to be addressed before we can expect to see these available in clinical practice. Some of the biggest challenges appear to be not so much related to what is technologically possible, but more about what wound parameters are the most importance to gather data on in order to aid wound healing. Furthermore, more research on critical thresholds

and time intervals for the measurements of these variables, in addition to a clearer understanding of how the interaction of various wound parameters should be interpreted, is critical to establish if the data is to add value to clinical practice.

This information needs to come from clinical research and be fed into the technical developers. Once this information is available, it seems that, despite the fact that there is still some way to go, most issues of a technical nature could feasibly be solved.<sup>681</sup>

In summary, NPWT devices could be seen as heading in three directions: increasingly complex devices for specialist applications within the hospital, progressively simpler devices for lower-cost settings such as the out-patient clinic or the home, and sensor-based devices with remote communication technologies to be used for distant monitoring.

It is yet unclear as to what the ultimate proportions of patients will be treated with each type of device.

## Changes in demand: supporting and constraining factors

How advanced and technological appealing a device might be is not the only determinant of how popular a medical device will be, as several stakeholders in the health-care delivery system will have the potential to influence whether or not a medical device is adopted into routine care or not. Payers at various levels of the system as well as clinicians and patients are driven by different rationales. There are several theories and models that describe and explain the mechanisms of how innovations diffuse into society; however, the evidence of it is complex.<sup>682</sup> The selected topics highlighted here are not based on a thorough and systematic analysis of the decisional environment around NPWT but simply based on a general

impression among the authors of the document as to what are the main issues that seem to be affecting and influencing future uptake of NPWT.

### Expanded indications

The technological developments in NPWT have already led to expansions of the indications of what types of wounds can benefit from NPWT treatment, compared with what was originally envisioned for devices first arriving in clinic. As examples, the availability of smaller, single-use disposable pumps has meant that new types of wounds can be treated (small, surgical) and in new settings such as short-term home care.<sup>683</sup> Adding to this, the new interventions underway as described earlier may even further contribute to the increased uptake.

### Increased focus on evidence and cost containment

Health-care providers are increasingly asking for evidence of a treatment's clinical effectiveness if they are going to provide reimbursement. In addition to this, some health-care systems are also starting to require health economic analysis providing an economic cost calculation in favour of the treatment mode.

The clinical benefits of NPWT in varied wound types has been reported in over 1000 peer-reviewed articles, and NPWT has been described as the gold standard in some areas of wound care. However, there is as yet no definitive clinical evidence supporting NPWT as a better and faster method for wound healing than the use of advanced dressing.<sup>683</sup>

This lack of strong evidence has several explanations. NPWT is a generic multimodal technology that can deliver a broad range of treatment goals depending on the patient being treated and these goals can be achieved by altering a range of variables which all add to the complexity of studying the therapy as part of an

RCT. The strict inclusion criteria in RCTs lead to recruitment problems and in turn limit real-world relevance and reproducibility.<sup>683</sup> When it comes to cost estimations, the natural variations in treatment outcomes combined with variations in regimes depending on the wound type, size, and amount of exudate, for example, makes it very difficult to come up with a solid figure that can be universally applied across health-care settings, wound types and patients. Underlying figures of importance for such calculations such as duration of treatment, number and frequency of dressing changes, training required, in combination with great variations in pricing models offered by the companies delivering the products are only examples of some of the key figures expected to vary between each individual case.

This lack of strong evidence could potentially become a hindrance for health-care providers' access to use NPWT as health authorities and payers are increasingly focusing on prioritisation and shifting of resources to treatment areas where a strong clinical evidence and health economic rationale can be proven.

This is already the case in England where 'The National Institute for Health and Care Excellence' (NICE) is well established and in Scandinavia where similar set ups are being discussed at political level. Also at the level of the individual clinicians the lack of evidence in some instances makes care givers reluctant to use this mode of therapy.<sup>683</sup>

On this background it becomes evident that the current problems relating to lack of high-level evidence supporting the clinical effectiveness of NPWT on different types of wounds can prove to become an important hindrance in terms of getting reimbursement for the treatment. This poses a barrier to access to the treatment. Thus, for the use of NPWT to gain in popularity and receive backing from health-care systems in the form of continued

reimbursement the issue of providing strong evidence need to be addressed.

### Changes in organisation of care and community care

A major and general trend across health-care settings around Europe is an increased move of specialised health-care services from in-hospital, ambulatory and acute health-care settings to community care.

Length of in hospital stay decreases and patients are transferred early to community care. This means that more complex and exuding wounds that would previously have been managed and taken care of by specialised staff in hospitals are now being cared for by community care nurses in the home setting. This in combination with the availability of smaller lightweight and disposable devices has led to an increased use of NPWT in community settings. Also the development within sensors-based systems with remote communication facilities might further support introduction of NPWT in community care settings.

To guarantee optimal usage of NPWT in the community settings future emphasis must focus on how to ensure that more nurses that do not have direct access to specialist health professionals for expert advice are able to handle the products correctly and are compliant to the prescribed treatment regimes. This requires training and availability of reliably support systems with easy access. If these aspects are not carefully dealt with this might impact treatment outcomes and potentially undermine the backing of the use of NPWT in the long run.

Also, the education of patients and caregivers becomes even more central when treatment with NPWT shifts towards the outpatient setting. Studies show that patients express the need for thorough education in managing the treatment.<sup>566,570</sup>

Therefore, it is important to educate patients and caregivers, not only to inform them which requires a structured teaching programme. Digital platforms and tools for self-treatment where patients and health professionals can communicate while being treated at home, development of telemedicine with NPWT is an interesting aspect for the future.

Another important aspect of this shift to community care is the adding of yet another complex layer of payer structures and decision making processes. The question about who will pay for the treatment, and when, will become even more complex to map as the answer to the question will differ according to the specific setup. This complexity and unclear roles of responsibilities might in the end affect the patients. It may delay appropriate care and lead to reluctance between decision making levels to take on the final responsibility of providing the most

optimal treatment if perceived expensive. In some cases it might not be the one having to pay for the treatment that will reap the potential economic benefit of providing it.

This shift of responsibility for more specialised care to community settings therefore calls for a need to rethink reimbursement models and furthermore increase pressure on safety aspects and training needs.

In the case of adoption of systems with remote monitoring facilities implementation barriers related to integration with existing electronic health records systems, changing care patterns (for example, insufficient staffing or time to monitor and follow-up on data) and professional roles (for example, clarify legal liability of responsibilities) will need to be addressed to be successful.<sup>684</sup>

# References

- 1** Bobkiewicz, A., Banasiewicz, T., Ledwosinski, W., Drews, M. Medical terminology associated with Negative Pressure Wound Therapy (NPWT). Understanding and misunderstanding in the field of NPWT. *Negative Pressure Wound Therapy*. 2014; 1: 2, 69–73.
- 2** Hampton, J. Providing cost-effective treatment of hard-to-heal wounds in the community through use of NPWT. *Br J Community Nurs* 2015; 20: Suppl 6, S14–S20.
- 3** Apelqvist, J., Armstrong, D.G., Lavery, L.A., Boulton, A.J. Resource utilization and economic costs of care based on a randomized trial of vacuum-assisted closure therapy in the treatment of diabetic foot wounds. *Am J Surg* 2008; 195: 6, 782–788.
- 4** Acosta, S., Bjarnason, T., Petersson, U. et al. Multicentre prospective study of fascial closure rate after open abdomen with vacuum and mesh-mediated fascial traction. *Br J Surg* 2011; 98: 5, 735–743.
- 5** Kaplan, M. Negative pressure wound therapy in the management of abdominal compartment syndrome. *Ostomy Wound Manage* 2005; 51: 2A Suppl, 29S–35S.
- 6** Swan, M., Banwell, P. Topical negative pressure. Advanced management of the open abdomen. *Oxford Wound Healing Society*. 2003.
- 7** Fuchs, U., Zittermann, A., Stuetzgen, B. et al. Clinical outcome of patients with deep sternal wound infection managed by vacuum-assisted closure compared to conventional therapy with open packing: a retrospective analysis. *Ann Thorac Surg* 2005; 79: 2, 526–531.
- 8** Fleck, T., Gustafsson, R., Harding, K. et al. The management of deep sternal wound infections using vacuum assisted closure? (V.A.C.®) therapy. *Int Wound J* 2006; 3: 4, 273–280.
- 9** Armstrong, D.G., Lavery, L.A., Diabetic Foot Study Consortium. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. *Lancet* 2005; 366: 9498, 1704–1710.
- 10** Blume, P.A., Walters, J., Payne, W. et al. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. *Diabetes Care* 2008; 31: 4, 631–636.
- 11** Trueman, P. Cost-effectiveness considerations for home health V.A.C. Therapy in the United States of America and its potential international application. *Int Wound J*. 2008; 5: Suppl 2, 23–26.
- 12** Dumville, J.C., Owens, G.L., Crosbie, E.J. et al. Negative pressure wound therapy for treating surgical wounds healing by secondary intention. *Cochrane Database Syst Rev* 2015; 6: 6, CD011278.
- 13** Dumville, J.C., Webster, J., Evans, D., Land, L. Negative pressure wound therapy for treating pressure ulcers. *Cochrane Database Syst Rev* 2015; 5: 5, CD011334.
- 14** Dumville, J.C., Hinchliffe, R.J., Cullum, N. et al. Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus. *Cochrane Database Syst Rev* 2013; 10: 10, CD010318.
- 15** Gottrup, F., Apelqvist, J., Price, P. et al. Outcomes in controlled and comparative studies on non-healing wounds: recommendations to improve the quality of evidence in wound management. *J Wound Care* 2010; 19: 6, 237–268.
- 16** Strohal, R., Apelqvist, J., Dissemond, J. et al. EWMA document: Debridement: an updated overview and clarification of the principle role of debridement. *J Wound Care* 2013; 22: Suppl 1, S1–S49.
- 17** Gottrup, F., Apelqvist, J., Bjarnsholt, T. et al. EWMA Document: Antimicrobials and Non-healing Wounds: Evidence, controversies and suggestions. *J Wound Care* 2013; 22: Suppl 5, S1–S89.
- 18** Moore, Z., Butcher, G., Corbett, L.Q. et al. EWMA Document: Home Care-Wound Care: Overview, Challenges and Perspectives. *J Wound Care* 2014; 23: Suppl 5; S1–S38.
- 19** Probst, S., Seppänen, S., Gethin, G. et al. EWMA Document: Home Care-Wound Care: Overview, Challenges and Perspectives. *J Wound Care* 2014; 23: Suppl 5a, S1–S41.
- 20** Rossi, P.G., Camilloni, L., Todini, A.R. et al. Health technology assessment of the negative pressure wound therapy for the treatment of acute and chronic wounds: Efficacy, safety, cost effectiveness, organizational and ethical impact. *Int J Public Health* 2012; 9: 2, 46–66.
- 21** Game, F.L., Apelqvist, J., Attinger, C. et al. (2015) IWGDF Guidance on use of interventions to enhance the healing of chronic ulcers of the foot in diabetes. International Working Group on Diabetic Foot. <http://preview.tinyurl.com/jd5pn2w> (accessed 15 February 2017)
- 22** Miller M. The Kremlin papers. *Technology Wound Journal*. 2008; 1: 22–24.
- 23** Fleischmann, W., Becker, U., Bischoff, M., Hoekstra, H. Vacuum sealing: indications, technique and results. *Eur J Orthop Surg Traumatol* 1995; 5: 37–40. Medline doi:10.1007/BF02716212
- 24** Morykwas, M.J., Argenta, L.C., Shelton-Brown, E.I., McGuirt, W. Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation. *Ann Plast Surg* 1997; 38: 6, 553–562.
- 25** Argenta, L.C., Morykwas, M.J. Vacuum-assisted closure: a new method for wound control and treatment: clinical experience. *Ann Plast Surg* 1997; 38: 6, 563–577.
- 26** Joseph, E., Hamori, C.A., Berman, S. et al. A prospective randomized trial of vacuum-assisted closure versus standard therapy of chronic nonhealing wounds. *Wounds*. 2000; 12: 3, 60–67.
- 27** McCallon, S.K., Knight, C.A., Valiulus, J.P. et al. Vacuum-assisted closure versus saline-moistened gauze in the healing of postoperative diabetic foot wounds. *Ostomy Wound Manage* 2000; 46: 8, 28–34.
- 28** Chariker, M.E., Jeter, K.F., Tintle, T.E., Bottsford, J.E. Effective management of incisional and cutaneous fistulae with closed suction wound drainage. *Contemp Surg* 1989; 34: 59–63.
- 29** Banwell, P.E., Téot, L. Topical negative pressure (TNP): the evolution of a novel wound therapy. *J Wound Care* 2003; 12: 1, 22–28.
- 30** Armstrong, D.G., Lavery, L.A., Abu-Rumman, P. et al. Outcomes of subatmospheric pressure dressing therapy on wounds of the diabetic foot. *Ostomy Wound Manage* 2002; 48: 4, 64–68.
- 31** Deva, A.K., Buckland, G.H., Fisher, E. et al. Topical negative pressure in wound management. *Med J Aust* 2000; 173: 3, 128–131.
- 32** Avery, C., Pereira, J., Moody, A., Whitworth, I. Clinical experience with the negative pressure wound dressing. *Br J Oral Maxillofac Surg* 2000; 38: 4, 343–345. Medline doi:10.1054/bjom.1999.0453
- 33** Banwell, P.E. Topical negative pressure therapy in wound care. *J Wound Care* 1999; 8: 2, 79–84.

- 34** Banwell, P, Holten, I, Martin, D.L. Negative pressure therapy: clinical applications and experience with 200 cases. *Wound Repair Regen* 1998; 6: 460.
- 35** Fleischmann, W, Lang, E, Russ, M. [Treatment of infection by vacuum sealing]. [Article in German] *Unfallchirurg* 1997; 100: 4, 301–304.
- 36** Fleischmann, W, Russ, M, Westhauser, A, Stampehl, M. [Vacuum sealing as carrier system for controlled local drug administration in wound infection]. [Article in German] *Unfallchirurg* 1998; 101: 8, 649–654.
- 37** Fleischmann, W, Suger, G, Kinzl, L. Treatment of bone and soft tissue defects in infected nonunion. *Acta Orthop Belg* 1992; 58 Suppl 1, 227–235.
- 38** Dunford, C.E. Treatment of a wound infection in a patient with mantle cell lymphoma. *Br J Nurs* 2001; 10: 16, 1058–1065.
- 39** Gerber-Haughton, R. et al. VAC-Therapie bei gasbildenden Anaerobiern. [The use of V.A.C. in gas producing anaerobic infections]. *ZfW* 2000; 5: 60–61.
- 40** Müller, G. [Vacuum dressing in septic wound treatment]. [Article in German] *Langenbecks Arch Chir Suppl Kongressbd* 1997; 114: 537–541.
- 41** Wongworawat, M.D., Schnall, S.B., Holtom, P.D. et al. Negative pressure dressings as an alternative technique for the treatment of infected wounds. *Clin Orthop Relat Res* 2003; 414: 414, 45–48. Medline doi:10.1097/01.blo.0000084400.53464.02.
- 42** Gupta, S, Gabriel, A., Lantis, J., Teot, L. Clinical recommendations and practical guide for negative pressure wound therapy with instillation. *Int Wound J* 2016; 13: 2, 159–174. Medline doi: 10.1111/iwj.12452.
- 43** Fluieraru, S, Bekara, F, Naud, M. et al. Sterile-water negative pressure instillation therapy for complex wounds and NPWT failures. *J Wound Care* 2013; 22: 6, 293–299.
- 44** Malmjö, M., Huddleston, E., Martin, R. Biological effects of a disposable, canisterless negative pressure wound therapy system. *Eplasty* 2014; 14: e15.
- 45** Levels of Evidence Oxford Centre for Evidence based Medicine (March 2009). <https://tinyurl.com/ochdj3q> (accessed 15 February 2017)
- 46** Feinstein, A.R., Horwitz, R.I. Problems in the evidence of evidence-based medicine. *Am J Med* 1997; 103: 6, 529–535.
- 47** Howes, N., Chagla, L., Thorpe, M., McCulloch, P. Surgical practice is evidence based. *Br J Surg* 1997; 84: 9, 1220–1223.
- 48** Stannard, J. Complex orthopaedic wounds: prevention and treatment with negative pressure wound therapy [back cover]. *Orthop Nurs* 2004; 23: Suppl 1, 3–10.
- 49** Falabella, A.F., Carson, P, Eaglstein, W.H., Falanga, V. The safety and efficacy of a proteolytic ointment in the treatment of chronic ulcers of the lower extremity. *J Am Acad Dermatol* 1998; 39: 5, 737–740.
- 50** Morykwas, M.J., Simpson, J., Pungler, K. et al. Vacuum-assisted closure: state of basic research and physiologic foundation. *Plast Reconstr Surg* 2006; 11: 7 Supplement, 1215–1265.
- 51** Kairinos, N., Solomons, M., Hudson, D.A. Negative-pressure wound therapy I: the paradox of negative-pressure wound therapy. *Plast Reconstr Surg* 2009; 123: 2, 589–600.
- 52** Kairinos, N., Solomons, M., Hudson, D.A. The paradox of negative pressure wound therapy – in vitro studies. *J Plast Reconstr Aesthet Surg* 2010; 63: 1, 174–179.
- 53** Webb, L.X. New techniques in wound management: vacuum-assisted wound closure. *J Am Acad Orthop Surg* 2002; 10: 5, 303–311.
- 54** Kamolz, L.P., Andel, H., Haslik, W. et al. Use of subatmospheric pressure therapy to prevent burn wound progression in human: first experiences. *Burns* 2004; 30: 3, 253–258.
- 55** Kubiak, B.D., Albert, S.P., Gatto, L.A. et al. Peritoneal negative pressure therapy prevents multiple organ injury in a chronic porcine sepsis and ischemia/reperfusion model. *Shock* 2010; 34: 5, 525–534.
- 56** Young, S.R., Hampton, S., Martin, R. Non-invasive assessment of negative pressure wound therapy using high frequency diagnostic ultrasound: oedema reduction and new tissue accumulation. *Int Wound J* 2013; 10: 4, 383–388.
- 57** Borgquist, O., Gustafsson, L., Ingemansson, R., Malmjö, M. Micro- and macromechanical effects on the wound bed of negative pressure wound therapy using gauze and foam. *Ann Plast Surg* 2010; 64: 6, 789–793. Medline doi:10.1097/SAP.0b013e3181ba578a.
- 58** Saxena, V., Hwang, C.W., Huang, S. et al. Vacuum-assisted closure: microdeformations of wounds and cell proliferation. *Plast Reconstr Surg* 2004; 114: 5, 1086–1096.
- 59** Greene, A.K., Puder, M., Roy, R. et al. Microdeformational wound therapy: effects on angiogenesis and matrix metalloproteinases in chronic wounds of 3 debilitated patients. *Ann Plast Surg* 2006; 56: 4, 418–422.
- 60** Wilkes, R., Zhao, Y., Kieswetter, K., Haridas, B. Effects of dressing type on 3D tissue microdeformations during negative pressure wound therapy: a computational study. *J Biomech Eng* 2009; 131: 3, 031012.
- 61** McNulty, A., Spranger, I., Courage, J. et al. The consistent delivery of negative pressure to wounds using reticulated, open cell foam and regulated pressure feedback. *Wounds* 2010; 22: 5, 114–120.
- 62** Wilkes, R., Zhao, Y., Cunningham, K. et al. 3D strain measurement in soft tissue: Demonstration of a novel inverse finite element model algorithm on MicroCT images of a tissue phantom exposed to negative pressure wound therapy. *J Mech Behav Biomed Mater* 2009; 2: 3, 272–287.
- 63** Kremers, L., Kearns, M., Hammon, D. et al. Involvement of mitogen activated protein kinases (MAP Kinases) in increased wound healing during subatmospheric pressure (SAP) treatment. *Wound Repair Regen* 2003; 11: 5, O009.
- 64** Chen, S.Z., Cao, D.Y., Li, J.Q., Tang, S.Y. [Effect of vacuum-assisted closure on the expression of proto-oncogenes and its significance during wound healing]. [Article in Chinese] *Zhonghua Zheng Xing Wai Ke Za Zhi* 2005; 21: 3, 197–200.
- 65** Vandenberg, H.H. Mechanical forces and their second messengers in stimulating cell growth in vitro. *Am J Physiol* 1992; 262: 3 Pt 2, R350–R355.
- 66** Sumpio, B.E., Banas, A.J. Response of porcine aortic smooth muscle cells to cyclic tensional deformation in culture. *J Surg Res* 1988; 44: 6, 696–701.
- 67** Sumpio, B.E., Banas, A.J., Levin, L.G., Johnson, G., Jr. Mechanical stress stimulates aortic endothelial cells to proliferate. *J Vasc Surg* 1987; 6: 3, 252–256.
- 68** Li, J., Hampton, T., Morgan, J.P., Simon, M. Stretch-induced VEGF expression in the heart. *J Clin Invest* 1997; 100: 1, 18–24.
- 69** Seko, Y., Seko, Y., Takahashi, N. et al. Pulsatile stretch stimulates vascular

- endothelial growth factor (VEGF) secretion by cultured rat cardiac myocytes. *Biochem Biophys Res Commun* 1999; 254: 2, 462–465.
- 70** Chang, H., Wang, B.W., Kuan, P., Shyu, K.G. Cyclical mechanical stretch enhances angiopoietin-2 and Tie2 receptor expression in cultured human umbilical vein endothelial cells. *Clin Sci* 2003; 104: 4, 421–428. doi:10.1042/cs1040421.
- 71** Cloutier, M., Maltais, F., Piedboeuf, B. Increased distension stimulates distal capillary growth as well as expression of specific angiogenesis genes in fetal mouse lungs. *Exp Lung Res* 2008; 34: 3, 101–113. Medline doi:10.1080/01902140701884331.
- 72** Labler, L., Rancan, M., Mica, L. et al. Vacuum-assisted closure therapy increases local interleukin-8 and vascular endothelial growth factor levels in traumatic wounds. *J Trauma Inj Infect Crit Care* 2009; 66: 3, 749–757.
- 73** Shiu, Y.T., Weiss, J.A., Hoying, J.B. et al. The role of mechanical stresses in angiogenesis. *Crit Rev Biomed Eng* 2005; 33: 5, 431–510. Medline doi:10.1615/CritRevBiomedEng.v33i5.10.
- 74** Ingber, D.E., Prusty, D., Sun, Z. et al. Cell shape, cytoskeletal mechanics, and cell cycle control in angiogenesis. *J Biomech* 1995; 28: 12, 1471–1484. Medline doi:10.1016/0021-9290(95)00095-X.
- 75** Von Offenberg Sweeney, N., Cummins, P.M., Cotter, E.J. et al. Cyclic strain-mediated regulation of vascular endothelial cell migration and tube formation. *Biochem Biophys Res Commun* 2005; 329: 2, 573–582.
- 76** Ingber, D.E. Tensegrity: the architectural basis of cellular mechanotransduction. *Annu Rev Physiol* 1997; 59: 1, 575–599.
- 77** Sadoshima, J., Takahashi, T., Jahn, L., Izumo, S. Roles of mechano-sensitive ion channels, cytoskeleton, and contractile activity in stretch-induced immediate-early gene expression and hypertrophy of cardiac myocytes. *Proc Natl Acad Sci USA* 1992; 89: 20, 9905–9909.
- 78** Sadoshima, J., Jahn, L., Takahashi, T. et al. Molecular characterization of the stretch-induced adaptation of cultured cardiac cells. An in vitro model of load-induced cardiac hypertrophy. *J Biol Chem* 1992; 267: 15, 10551–10560.
- 79** Sadoshima, J., Izumo, S. Mechanical stretch rapidly activates multiple signal transduction pathways in cardiac myocytes: potential involvement of an autocrine/paracrine mechanism. *EMBO J* 1993; 12: 4, 1681–1692.
- 80** Baudouin-Legros, M., Paquet, J.L., Brunelle, G., Meyer, P. Role of nuclear proto-oncogenes in the proliferation of aortic smooth muscle cells in spontaneously hypertensive rats. *J Hypertens* 1989; 7: 6, S114–S115.
- 81** Folkman, J., Moscona, A. Role of cell shape in growth control. *Nature* 1978; 273: 5661, 345–349.
- 82** Younan, G., Ogawa, R., Ramirez, M. et al. Analysis of nerve and neuropeptide patterns in vacuum-assisted closure-treated diabetic murine wounds. *Plast Reconstr Surg* 2010; 126: 1, 87–96.
- 83** Ingber, D.E., Huang, S. The structural and mechanical complexity of cell-growth control. *Nat Cell Biol* 1999; 1: 5, E131–E138.
- 84** Huang, S., Chen, C.S., Ingber, D.E. Control of cyclin D1, p27(Kip1), and cell cycle progression in human capillary endothelial cells by cell shape and cytoskeletal tension. *Mol Biol Cell* 1998; 9: 11, 3179–3193.
- 85** Chen, C.S., Mirsich, M., Huang, S. et al. Geometric control of cell life and death. *Science* 1997; 276: 5317, 1425–1428.
- 86** Fleck, T.M., Fleck, M., Moidl, R. et al. The vacuum-assisted closure system for the treatment of deep sternal wound infections after cardiac surgery. *Ann Thorac Surg* 2002; 74: 5, 1596–1600.
- 87** Fleischmann W, Lang E, Kinzl L. [Vacuum assisted wound closure after dermatofasciotomy of the lower extremity]. [Article in German] *Unfallchirurg* 1996; 99: 4, 283–287.
- 88** Lohman, R.F., Lee, R.C. Discussion: vacuum assisted closure: microdeformations of wounds and cell proliferation. *Plast Reconstr Surg* 2004; 114: 5, 1097–1098.
- 89** Morykwas, M.J., Argenta, L.C. Nonsurgical modalities to enhance healing and care of soft tissue wounds. *J South Orthop Assoc* 1997; 6: 4, 279–288.
- 90** Jungius, K.P., Chilla, B.K., Labler, L. et al. [Non-invasive assessment of the perfusion of wounds using power Doppler imaging: vacuum assisted closure versus direct wound closure]. [Article in German] *Ultraschall Med* 2006; 27: 5, 473–477.
- 91** Rejzek, A., Weyer, F. The use of the V.A.C.™ system in the therapy of ulcer cruris and diabetic gangrene. *Acta Chir Austriaca. Supplement* 1998; 150: 12–13.
- 92** Timmers, M.S., Le Cessie, S., Barwell, P., Jukema, G.N. The effects of varying degrees of pressure delivered by negative-pressure wound therapy on skin perfusion. *Ann Plast Surg* 2005; 55: 6, 665–671. Medline doi:10.1097/01.sap.0000187182.90907.3d.
- 93** Wackenfors, A., Sjögren, J., Gustafsson, R. et al. Effects of vacuum-assisted closure therapy on inguinal wound edge microvascular blood flow. *Wound Repair Regen* 2004; 12: 6, 600–606.
- 94** De Lange, M.Y., Nicolai, J.P. The influence of subatmospheric pressure on tissue oxygenation and temperature. Abstract volume 2nd WUWH Meeting, 2004; Paris 2004: 51.
- 95** Barwell, P.E., Morykwas, M.J., Jennings, D.A. Dermal microvascular blood flow in experimental partial thickness burns: the effect of topical sub-atmospheric pressure. *J Burn Care Rehabil* 2000; 21: 161.
- 96** Schrank, C., Mayr, M., Overesch, M. et al. [Results of vacuum therapy (v.a.c.) of superficial and deep dermal burns]. [Article in German] *Zentralbl Chir* 2004; 129 Suppl 1: S59–S61.
- 97** Chen, S.Z., Li, J., Li, X.Y., Xu, L.S. Effects of vacuum-assisted closure on wound microcirculation: an experimental study. *Asian J Surg* 2005; 28: 3, 211–217.
- 98** Wackenfors, A., Gustafsson, R., Sjögren, J. et al. Blood flow responses in the peristernal thoracic wall during vacuum-assisted closure therapy. *Ann Thorac Surg* 2005; 79: 5, 1724–1730.
- 99** Petzina, R., Gustafsson, L., Mokhtari, A. et al. Effect of vacuum-assisted closure on blood flow in the peristernal thoracic wall after internal mammary artery harvesting. *Eur J Cardiothorac Surg* 2006; 30: 1, 85–89.
- 100** Petzina, R., Ugander, M., Gustafsson, L. et al. Topical negative pressure therapy of a sternotomy wound increases sternal fluid content but does not affect internal thoracic artery blood flow: Assessment using magnetic resonance imaging. *J Thorac Cardiovasc Surg* 2008; 135: 5, 1007–1013.
- 101** Ichioka, S., Watanabe, H., Sekiya, N. et al. A technique to visualize wound bed microcirculation and the acute effect of negative pressure. *Wound Repair Regen* 2008; 16: 3, 460–465.
- 102** Horch, R.E., Muchow, S., Dragu, A. Erste Zwischenergebnisse der Perfusionsbeeinflussung durch Prevena: Gewebsperfusion. *Dzf* 2012; 16: 1–3.
- 103** Hudlicka, O., Brown, M., Egginton, S. Angiogenesis in skeletal and cardiac muscle. *Physiol Rev* 1992; 72: 2, 369–417.
- 104** Sano, H., Ichioka, S. Involvement of nitric oxide in the wound bed microcirculatory change during negative pressure wound therapy. *Int Wound J* 2015; 12: 4, 397–401.



- 105** Ping, A., Zhang, T., Ren, B. et al. Effect of vacuum-assisted closure combined with open bone grafting to promote rabbit bone graft vascularization. *Med Sci Monit* 2015;21:1200–1206. Medline doi:10.12659/MSM.892939.
- 106** Genecov, D.G., Schneider, A.M., Morykwas, M.J. et al. A controlled subatmospheric pressure dressing increases the rate of skin graft donor site reepithelialization. *Ann Plast Surg* 1998; 40: 3, 219–225. Medline doi:10.1097/0000637-199803000-00004.
- 107** Erba, P., Ogawa, R., Ackermann, M. et al. Angiogenesis in wounds treated by microdeformational wound therapy. *Ann Surg* 2011; 253: 2, 402–409. Medline doi:10.1097/SLA.0b013e31820563a8.
- 108** Mouës, C.M., Vos, M.C., Van Den Bemd, G.J. et al. Bacterial load in relation to vacuum-assisted closure wound therapy: A prospective randomized trial. *Wound Repair Regen* 2004; 12: 1, 11–17.
- 109** Yusuf, E., Jordan, X., Clauss, M. et al. High bacterial load in negative pressure wound therapy (NPWT) foams used in the treatment of chronic wounds. *Wound Repair Regen* 2013; 21: 5, 677–681.
- 110** Weed, T., Ratliff, C., Drake, D.B. Quantifying bacterial bioburden during negative pressure wound therapy: does the wound VAC enhance bacterial clearance? *Ann Plast Surg* 2004; 52: 3, 276–279.
- 111** James, G.A., Swogger, E., Wolcott, R. et al. Biofilms in chronic wounds. *Wound Repair Regen* 2008; 16: 1, 37–44.
- 112** Wolcott, R.D., Rumbaugh, K.P., James, G. et al. Biofilm maturity studies indicate sharp debridement opens a time-dependent therapeutic window. *J Wound Care* 2010; 19: 8, 320–328.
- 113** Gouttefangeas, C., Eberle, M., Ruck, P. et al. Functional T lymphocytes infiltrate implanted polyvinyl alcohol foams during surgical wound closure therapy. *Clin Exp Immunol* 2001; 124: 3, 398–405.
- 114** Adams, T.S., Herrick, S., McGrouther, D.A. VAC-therapy alters the number and distribution of neutrophils in acute dermal wounds. In: Banwell, P.T. (ed). Topical negative pressure (TNP) focus group meeting (Proceedings European Tissue Repair Society). TXP Communications: 212; 2004.
- 115** Buttenschoen, K., Fleischmann, W., Haupt, U. et al. The influence of vacuum-assisted closure on inflammatory tissue reactions in the postoperative course of ankle fractures. *Foot Ankle Surg* 2001; 7: 3, 165–173.
- 116** Kilpadi, D.V., Bower, C.E., Reade, C.C. et al. Effect of Vacuum Assisted Closure Therapy on early systemic cytokine levels in a swine model. *Wound Repair Regen* 2006; 14: 2, 210–215.
- 117** Labler, L., Mica, L., Härter, L. et al. [Influence of V.A.C.-therapy on cytokines and growth factors in traumatic wounds]. [Article in German] *Zentralbl Chir* 2006; 131 Suppl 1: S62–S67.
- 118** Tautenhahn, J., Bürger, T., Lippert, H. [The present state of vacuum sealing]. [Article in German] *Chirurg* 2004; 75: 5, 492–497.
- 119** Walgenbach, K.J., Stark, J.B. Induction of angiogenesis following vacuum sealing. *J Wound Healing* 2000; 13: 9–10.
- 120** Kopp, J., Hoff, C., Rosenberg, B. et al. Application of VAC therapy upregulates growth factor levels in neuropathic diabetic foot ulcers. *Wound Repair Regen* 2003; 11: 5, 0007.
- 121** Chesnoy, S., Lee, P.Y., Huang, L. Intradermal injection of transforming growth factor-beta 1 gene enhances wound healing in genetically diabetic mice. *Pharm Res* 2003; 20: 3, 345–350.
- 122** Galiano, R.D., Tepper, O.M., Pelo, C.R. et al. Topical vascular endothelial growth factor accelerates diabetic wound healing through increased angiogenesis and by mobilizing and recruiting bone marrow-derived cells. *Am J Pathol* 2004; 164: 6, 1935–1947.
- 123** Hom, D.B., Manivel, J.C. Promoting healing with recombinant human platelet-derived growth factor BB in a previously irradiated problem wound. *Laryngoscope* 2003; 113: 9, 1566–1571.
- 124** Sun, T.Z., Fu, X.B., Zhao, Z.L. G et al. [Experimental study on recombinant human platelet-derived growth factor gel in a diabetic rat model of cutaneous incisional wound healing]. [Article in Chinese] *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue* 2003; 15: 10, 596–599.
- 125** Uhl, E., Rösken, F., Sirsjo, A., Messmer, K. Influence of platelet-derived growth factor on microcirculation during normal and impaired wound healing. *Wound Repair Regen* 2003 Sep; 11(5):361–367.
- 126** Van Den Boom, R., Wilmsink, J.M., Okane, S. et al. Transforming growth factor-beta levels during second-intention healing are related to the different course of wound contraction in horses and ponies. *Wound Repair Regen* 2002; 10: 3, 188–194.
- 127** Kohase, M., May, L.T., Tamm, I. et al. A cytokine network in human diploid fibroblasts: interactions of beta-interferons, tumor necrosis factor, platelet-derived growth factor, and interleukin-1. *Mol Cell Biol* 1987; 7: 1, 273–280.
- 128** Ramanathan, M. A pharmacokinetic approach for evaluating cytokine binding macromolecules as antagonists. *Pharm Res* 1996; 13: 1, 84–90.
- 129** Tarnawski, A. Molecular mechanisms of ulcer healing. *Drug News Perspect* 2000; 13: 3, 158–168.
- 130** Succar, J., Douaiher, J., Lancerotto, L. et al. The role of mouse mast cell proteases in the proliferative phase of wound healing in microdeformational wound therapy. *Plast Reconstr Surg* 2014; 134: 3, 459–467.
- 131** Glass, G.E., Murphy, G.F., Esmaeili, A. et al. Systematic review of molecular mechanism of action of negative-pressure wound therapy. *Br J Surg* 2014; 101: 13, 1627–1636.
- 132** Hsu, C.C., Chow, S.E., Chen, C.P. et al. Negative pressure accelerated monolayer keratinocyte healing involves Cdc42 mediated cell podia formation. *J Dermatol Sci* 2013; 70: 3, 196–203.
- 133** Yang, F., Hu, D., Bai, X.J., et al. [The influence of oxygen partial pressure change and vascularization of rabbit wound through negative pressure wound therapy]. [Article in Chinese] *Zhonghua Wai Ke Za Zhi* 2012; 50: 7, 650–654.
- 134** Jacobs, S., Simhaee, D.A., Marsano, A. et al. Efficacy and mechanisms of vacuum-assisted closure (VAC) therapy in promoting wound healing: a rodent model. *J Plast Reconstr Aesthet Surg* 2009; 62: 10, 1331–1338.
- 135** Nuutila, K., Siltanen, A., Peura, M. et al. Gene expression profiling of negative-pressure-treated skin graft donor site wounds. *Burns* 2013; 39: 4, 687–693.
- 136** Yang, S.L., Han, R., Liu, Y. et al. Negative pressure wound therapy is associated with up-regulation of bFGF and ERK1/2 in human diabetic foot wounds. *Wound Repair Regen* 2014; 22: 4, 548–554.
- 137** Liu, D., Zhang, L., Li, T. et al. Negative-pressure wound therapy enhances local inflammatory responses in acute infected soft-tissue wound. *Cell Biochem Biophys* 2014; 70: 1, 539–547.
- 138** Coutin, J.V., Lanz, O.I., Magnin-Bissel, G.C. et al. Cefazolin concentration in surgically created wounds treated with negative pressure wound therapy compared to surgically created wounds treated with nonadherent wound dressings. *Vet Surg* 2015; 44: 1, 9–16.
- 139** Birke-Sorensen, H., Malmjö, M., Rome, P. et al. Evidence-based

- recommendations for negative pressure wound therapy: treatment variables (pressure levels, wound filler and contact layer) – Steps towards an international consensus. *J Plast Reconstr Aesthet Surg* 2011; 64: Suppl, S1–S16.
- 140** Torbrand, C., Ingemansson, R, Gustafsson, L et al. Pressure transduction to the thoracic cavity during topical negative pressure therapy of a sternotomy wound. *Int Wound J* 2008; 5: 4, 579–584.
- 141** Petzina, R, Ugander, M., Gustafsson, L et al. Hemodynamic effects of vacuum-assisted closure therapy in cardiac surgery: Assessment using magnetic resonance imaging. *J Thorac Cardiovasc Surg* 2007; 133: 5, 1154–1162.
- 142** Cheng, B., Fu, X.B., Gu, X.M. et al. [The regulation mechanisms of MMP-1,2 and TIMP-1,2 on wound healing after partial thickness scald]. [Article in Chinese] *Zhonghua Wai Ke Za Zhi* 2003; 41: 10, 766–769.
- 143** Cook, H., Stephens, P, Davies, KJ, et al. Defective extracellular matrix reorganization by chronic wound fibroblasts is associated with alterations in TIMP-1, TIMP-2, and MMP-2 activity. *J Invest Dermatol* 2000; 115: 2, 225–233.
- 144** Maier, D, Beck, A., Kinzl, L, Bischoff, M. [The physics of vacuum therapy]. [Article in German] *Zentralbl Chir* 2005; 130: 5, 463–468.
- 145** Von Lübken, F, Von Thun-Hohenstein, H., Weymouth, M., et al. [Pressure conditions under VVS-foams—an experimental in-vitro- and in-vivo-analysis]. [Article in German] *Zentralbl Chir* 2004; 129: Suppl 1, S95–S97.
- 146** Willy, C., von Thun-Hohenstein, H., von Lübken, F et al. [Experimental principles of the V.A.C.-therapy pressure values in superficial soft tissue and the applied foam]. [Article in German] *Zentralbl Chir* 2006; 131: Suppl 1, S50–S61.
- 147** Eisenhardt, S.U., Schmidt, Y., Thiele, J.R. et al. Negative pressure wound therapy reduces the ischaemia/reperfusion-associated inflammatory response in free muscle flaps. *J Plast Reconstr Aesthet Surg* 2012; 65: 5, 640–649.
- 148** Isago, T., Nozaki, M., Kikuchi, Y. et al. Effects of different negative pressures on reduction of wounds in negative pressure dressings. *J Dermatol* 2003; 30: 8, 596–601.
- 149** Morykwas, M.J., Falser, B.J., Pearce, D.J., Argenta, L.C. Effects of varying levels of subatmospheric pressure on the rate of granulation tissue formation in experimental wounds in swine. *Ann Plast Surg* 2001; 47: 5, 547–551.
- 150** Borgquist, O., Ingemansson, R., Malmjö, M. Wound edge microvascular blood flow during negative-pressure wound therapy: examining the effects of pressures from –10 to –175 mmHg. *Plast Reconstr Surg* 2010; 125: 2, 502–509.
- 151** Borgquist, O., Gustafson, L., Ingemansson, R., Malmjö, M. Tissue ingrowth into foam but not into gauze during negative pressure wound therapy. *Wounds* 2009; 21: 11, 302–309.
- 152** Nease, C. Using low pressure, NPWT for wound preparation & the management of split-thickness skin grafts in 3 patients with complex wound. *Ostomy Wound Manage* 2009; 55: 6, 32–42.
- 153** Zhou, M., Yu, A., Wu, G. et al. Role of different negative pressure values in the process of infected wounds treated by vacuum-assisted closure: an experimental study. *Int Wound J* 2013; 10: 5, 508–515.
- 154** Bollero, D., Camino, R., Risso, D et al. Acute complex traumas of the lower limbs: a modern reconstructive approach with negative pressure therapy. *Wound Repair Regen* 2007; 15: 4, 589–594.
- 155** Borgquist, O., Ingemansson, R., Malmjö, M. Individualizing the use of negative pressure wound therapy for optimal wound healing: a focused review of the literature. *Ostomy Wound Manage* 2011; 57: 4, 44–54.
- 156** Hurd, T., Chadwick, P., Cote, J. et al. Impact of gauze-based NPWT on the patient and nursing experience in the treatment of challenging wounds. *Int Wound J* 2010; 7: 6, 448–455.
- 157** Jeffery, S.L. Advanced wound therapies in the management of severe military lower limb trauma: a new perspective. *Eplasty* 2009; 9: e28.
- 158** Kairinos, N., Voogd, A.M., Botha, P.H. et al. Negative-pressure wound therapy II: negative-pressure wound therapy and increased perfusion. Just an illusion? *Plast Reconstr Surg* 2009; 123: 2, 601–612.
- 159** Mendez-Eastman, S. Guidelines for using negative pressure wound therapy. *Adv Skin Wound Care* 2001; 14: 6, 314–22.
- 160** Stannard, J.P., Robinson, J.T., Anderson, E.R. et al. Negative pressure wound therapy to treat hematomas and surgical incisions following high-energy trauma. *J Trauma Inj Infect Crit Care* 2006; 60: 6, 1301–1306.
- 161** Fong, K.D., Hu, D., Eichstadt, S. et al. The SNaP system: biomechanical and animal model testing of a novel ultraportable negative-pressure wound therapy system. *Plast Reconstr Surg* 2010; 125: 5, 1362–1371.
- 162** Armstrong, D.G., Marston, W.A., Reyzelman, A.M., Kirsner, R.S. Comparison of negative pressure wound therapy with an ultraportable mechanically powered device vs. traditional electrically powered device for the treatment of chronic lower extremity ulcers: A multicenter randomized-controlled trial. *Wound Repair Regen* 2011; 19: 2, 173–180.
- 163** Armstrong, D.G., Marston, W.A., Reyzelman, A.M., Kirsner, R.S. Comparative effectiveness of mechanically and electrically powered negative pressure wound therapy devices: A multicenter randomized controlled trial. *Wound Repair Regen* 2012; 20: 3, 332–341.
- 164** Hutton, D.W., Sheehan, P. Comparative effectiveness of the SNaP™ Wound Care System. *Int Wound J* 2011; 8: 2, 196–205.
- 165** Lerman, B., Oldenbrook, L., Eichstadt, S.L. et al. Evaluation of chronic wound treatment with the SNaP wound care system versus modern dressing protocols. *Plast Reconstr Surg* 2010; 126: 4, 1253–1261.
- 166** Lerman, B., Oldenbrook, L., Ryu, J. et al. The SNaP Wound Care System: a case series using a novel ultraportable negative pressure wound therapy device for the treatment of diabetic lower extremity wounds. *J Diabetes Sci Tech* 2010; 4: 4, 825–830.
- 167** Marston, W.A., Armstrong, D.G., Reyzelman, A.M., Kirsner, R.S. A multicenter randomized controlled trial comparing treatment of venous leg ulcers using mechanically versus electrically powered negative pressure wound therapy. *Adv Wound Care* 2015; 4: 2, 75–82.
- 168** Lee, K.N., Ben-Nakhi, M., Park, E.J., Hong, J.P. Cyclic negative pressure wound therapy: an alternative mode to intermittent system. *Int Wound J* 2013; 2: 6, 686–92.
- 169** Malmjö, M., Ingemansson, R. Variable, intermittent and continuous negative pressure wound therapy using foam or gauze: the biological effects on the wound bed including, blood flow, micro and macro deformation, granulation tissue quantity, wound bed character. Symposium on Advanced Wound Care and the Wound Healing Society Meeting; 2010 17-20 April; Orlando, Florida.
- 170** Borgquist, O., Ingemansson, R., Malmjö, M. The effect of intermittent and variable negative pressure wound therapy on wound edge microvascular blood flow. *Ostomy Wound Manage* 2010; 56: 3, 60–67.
- 171** Fujiwara, T., Nishimoto, S., Ishise, H. et al. Influence of continuous or intermittent negative pressure on bacterial proliferation potency in vitro. *J Plast Surg Hand Surg* 2013; 47: 3, 180–184.
- 172** Ahearn, C. Intermittent NPWT and lower negative pressure exploring

the disparity between science and current practice: a review. *Ostomy Wound Manage* 2009; 55: 6, 22–28.

**173** Chariker, M.E., Gerstle, T.L., Morrison, C.S. An algorithmic approach to the use of gauze-based negative-pressure wound therapy as a bridge to closure in pediatric extremity trauma. *Plast Reconstr Surg* 2009; 123: 5, 1510–1520.

**174** Campbell, P.E., Smith, G.S., Smith, J.M. Retrospective clinical evaluation of gauze-based negative pressure wound therapy. *Int Wound J* 2008; 5: 2, 280–286.

**175** Fraccalvieri, M., Scalise, A., Ruka, E. et al. Negative pressure wound therapy using gauze and foam: histological, immunohistochemical, and ultrasonography morphological analysis of granulation and scar tissues. *Eur J Plast Surg* 2014; 37: 8, 411–416.

**176** Fraccalvieri, M., Zingarelli, E., Ruka, E. et al. Negative pressure wound therapy using gauze and foam: histological, immunohistochemical and ultrasonography morphological analysis of the granulation tissue and scar tissue. Preliminary report of a clinical study. *Int Wound J* 2011; 8: 4, 355–364.

**177** Malmjö, M., Ingemansson, R., Martin, R., Huddleston, E. Negative-pressure wound therapy using gauze or open-cell polyurethane foam: Similar early effects on pressure transduction and tissue contraction in an experimental porcine wound model. *Wound Repair Regen* 2009; 17: 2, 200–205.

**178** Malmjö, M., Lindstedt, S., Ingemansson, R. Influence on pressure transduction when using different drainage techniques and wound fillers (foam and gauze) for negative pressure wound therapy. *Int Wound J* 2010; 7: 5, 706–712.

**179** Malmjö, M., Ingemansson, R., Lindstedt, S., Gustafsson, L. Comparison of bacteria and fungus-binding mesh, foam and gauze as fillers in negative pressure wound therapy—pressure transduction, wound edge contraction, microvascular blood flow and fluid retention. *Int Wound J* 2013; 10: 5, 597–605.

**180** Malmjö, M., Lindstedt, S., Ingemansson, R. Effects of foam or gauze on sternum wound contraction, distension and heart and lung damage during negative-pressure wound therapy of porcine sternotomy wounds. *Interact Cardiovasc Thorac Surg* 2011; 12: 3, 349–354.

**181** Jeffery, S.L. Advanced wound therapies in the management of severe military lower limb trauma: a new perspective. *Eplasty* 2009; 9: e28.

**182** Borgquist, O., Ingemansson, R., Malmjö, M. The influence of low and high pressure levels during negative-pressure wound therapy on wound contraction and fluid evacuation. *Plast Reconstr Surg* 2011; 127: 2, 551–559.

**183** Malmjö, M., Ingemansson, R. Similar biological effects of green and black polyurethane foam in negative pressure wound therapy. 20th Conference of the European Wound Management Association; Geneva, Switzerland, 2010.

**184** Anesäter, E., Borgquist, O., Hedström, E. et al. The influence of different sizes and types of wound fillers on wound contraction and tissue pressure during negative pressure wound therapy. *Int Wound J* 2011; 8: 4, 336–342.

**185** Lambert, K.V., Hayes, P., McCarthy, M. Vacuum assisted closure: a review of development and current applications. *Eur J Vasc Endovasc Surg* 2005; 29: 3, 219–226.

**186** Malmjö, M., Lindstedt, S., Ingemansson, R., Gustafsson, L. Use of bacteria- and fungus-binding mesh in negative pressure wound therapy provides significant granulation tissue without tissue ingrowth. *Eplasty* 2014; 14: e3.

**187** Fraccalvieri, M., Ruka, E., Bocchiotti, M.A. et al. Patient's pain feedback using negative pressure wound therapy with foam and gauze. *Int Wound J* 2011; 8: 5, 492–499.

**188** Malmjö, M., Gustafsson, L., Lindstedt, S., Ingemansson, R. Negative pressure wound therapy-associated tissue trauma and pain: a controlled in vivo study comparing foam and gauze dressing removal by immunohistochemistry for substance P and calcitonin gene-related peptide in the wound edge. *Ostomy Wound Manage* 2011; 57: 12, 30–35.

**189** Jeffery, S.L. The use of an antimicrobial primary wound contact layer as liner and filler with NPWT. *J Wound Care* 2014; 23: 8 (Suppl), S3–S14.

**190** Blakely, M., Weir, D. The innovative use of Safetac soft silicone in conjunction with negative pressure wound therapy: three case studies. Symposium on Advanced Wound Care; Tampa, FL, 2007.

**191** Dunbar, A., Bowers, D.M., Holderness, H., Jr. Silicone net dressing as an adjunct with negative pressure wound therapy. *Ostomy Wound Manage* 2005; 51: 11A (Suppl), 21-2.

**192** Krasner, D.L. Managing wound pain in patients with vacuum-assisted closure devices. *Ostomy Wound Manage* 2002; 48: 5, 38–43.

**193** Terrazas, S.G. Adjuvant dressing for negative pressure wound therapy in burns. *Ostomy Wound Manage* 2006; 52: 1, 16–18.

**194** Malmjö, M., Borgquist, O. NPWT settings and dressing choices made easy. *Wounds International* 2010; 1: 3, 1–6.

**195** Potter, M.J., Banwell, P., Baldwin, C. et al. In vitro optimisation of topical negative pressure regimens for angiogenesis into synthetic dermal replacements. *Burns* 2008; 34: 2, 164–174.

**196** Pollard, R.L., Kennedy, P.J., Maitz, P.K. The use of artificial dermis (Integra) and topical negative pressure to achieve limb salvage following soft-tissue loss caused by meningococcal septicaemia. *J Plast Reconstr Aesthet Surg* 2008; 61: 3, 319–322. M

**197** Goutos, I., Ghosh, S.J. Gauze-based negative pressure wound therapy as an adjunct to collagen-elastin dermal template resurfacing. *J Wound Care* 2011; 20: 2, 55–60.

**198** Kahn, S.A., Beers, R.J., Lentz, C.W. Use of acellular dermal replacement in reconstruction of nonhealing lower extremity wounds. *J Burn Care Res* 2011; 32: 1, 124–128. 7

**199** de Runz, A., Zuily, S., Gosset, J. et al. Particular catastrophic antiphospholipid syndrome, on the sole surgical site after breast reduction. *J Plast Reconstr Aesthet Surg* 2013; 66: 11, e321–e324.

**200** Greenwood, J.E., Mackie, I.P. Neck contracture release with matriderm collagen/elastin dermal matrix. *Eplasty* 2011; 11: e16.

**201** Fraccalvieri, M., Pristerà, G., Zingarelli, E. et al. Treatment of chronic heel osteomyelitis in vasculopathic patients. Can the combined use of Integra®, skin graft and negative pressure wound therapy be considered a valid therapeutic approach after partial tangential calcaneotomy? *Int Wound J* 2012; 9: 2, 214–220.

**202** Abbas Khan, M.A., Chipp, E., Hardwicke, J. et al. The use of Dermal Regeneration Template (Integra®) for reconstruction of a large full-thickness scalp and calvarial defect with exposed dura. *J Plast Reconstr Aesthet Surg* 2010; 63: 12, 2168–2171.

**203** Atlan, M., Naouri, M., Lorette, G. et al. [Original treatment of constitutional painful callosities by surgical excision, collagen/elastin matrix (MatriDerm®) and split thickness skin graft secured by negative wound therapy]. [Article in French] *Ann Chir Plast Esthet* 2011; 56: 2, 163–169.

**204** Verbelen, J., Hoeksema, H., Pirayesh, A. Exposed tibial bone after burns: Flap reconstruction versus dermal substitute. *Burns* 2016; 42: 2, e31–e37.

**205** González Alaña, I., Torrero López, J.V., Martín Playá, P., Gabilondo

- Zubizarreta, F.J. Combined use of negative pressure wound therapy and Integra® to treat complex defects in lower extremities after burns. *Ann Burns Fire Disasters* 2013; 26: 2, 90-93.
- 206** Abu-Omar, Y., Naik, M.J., Catarino, P.A., Ratnatunga, C. Right ventricular rupture during use of high-pressure suction drainage in the management of poststernotomy mediastinitis. *Ann Thorac Surg* 2003; 76: 3, 974. [author reply 975]
- 207** Sartipy, U., Lockowandt, U., Gäbel, J. et al. Cardiac rupture during vacuum-assisted closure therapy. *Ann Thorac Surg* 2006; 82: 3, 1110-1111.
- 208** Yellin, A., Refaely, Y., Paley, M., Simansky, D. Major bleeding complicating deep sternal infection after cardiac surgery. *J Thorac Cardiovasc Surg* 2003; 125: 3, 554-558.
- 209** Sjögren, J., Gustafsson, R., Nilsson, J. et al. Negative-pressure wound therapy following cardiac surgery: bleeding complications and 30-day mortality in 176 patients with deep sternal wound infection. *Interact Cardiovasc Thorac Surg* 2011; 12: 2, 117-120.
- 210** Petzina, R., Malmjö, M., Stamm, C., Hetzer, R. Major complications during negative pressure wound therapy in poststernotomy mediastinitis after cardiac surgery. *J Thorac Cardiovasc Surg* 2010; 140: 5, 1133-1136.
- 211** Khoynzhad, A., Abbas, G., Palazzo, R.S., Graver, L.M. Spontaneous right ventricular disruption following treatment of sternal infection. *J Card Surg* 2004; 19: 1, 74-78.
- 212** Grauhan, O., Navasadyan, A., Hussmann, J., Hetzer, R. Infectious erosion of aorta ascendens during vacuum-assisted therapy of mediastinitis. *Interact Cardiovasc Thorac Surg* 2010; 11: 4, 493-494.
- 213** Ennker, I.C., Malkoc, A., Pietrowski, D. et al. The concept of negative pressure wound therapy (NPWT) after poststernotomy mediastinitis—a single center experience with 54 patients. *J Cardiothorac Surg* 2009; 4: 1, 5.
- 214** Camero-Alcázar, M., Silva Guisasaola, J.A., Rodríguez Hernández, J.E. eComment: Right ventricle bleeding secondary to vacuum assisted therapy? *Interact Cardiovasc Thorac Surg* 2010; 10: 3, 472.
- 215** Caianiello, G., Petraio, A., Ursomando, F. et al. Aortic erosion during negative pressure therapy in a pediatric heart transplant recipient. *Ann Thorac Surg* 2011; 92: 5, 1879-1880.
- 216** Bapat, V., El-Muttardi, N., Young, C. et al. Experience with Vacuum-assisted closure of sternal wound infections following cardiac surgery and evaluation of chronic complications associated with its use. *J Card Surg* 2008; 23: 3, 227-233.
- 217** Sumpio, B.E., Allie, D.E., Horvath, K.A. et al. Role of negative pressure wound therapy in treating peripheral vascular graft infections. *Vascular* 2008; 16: 4, 194-200.
- 218** Cheng, H.T., Hsu, Y.C., Wu, C.I. Efficacy and safety of negative pressure wound therapy for Szilagyi grade III peripheral vascular graft infection: Table 1. *Interact Cardiovasc Thorac Surg* 2014; 19: 6, 1048-1052.
- 219** Ren, H., Li, Y. Severe complications after negative pressure wound therapy in burned wounds: two case reports. *Therapeutics and Clinical Risk Management* 2014; 10: 513-516.
- 220** US Food and Drug Administration (FDA). UPDATE on Serious Complications Associated with Negative Pressure Wound Therapy Systems: FDA Safety Communication 2011 <https://tinyurl.com/xjvtun> (accessed 1 March 2017).
- 221** US Food and Drug Administration (FDA). Serious complications associated with negative pressure wound therapy systems 2009 (<http://www.fda.gov/medicaldevices/safety/alertsandnotices/publichealthnotifications/> ucm190658.htm)
- 222** Petzina, R., Hoffmann, J., Navasadyan, A. et al. Negative pressure wound therapy for post-sternotomy mediastinitis reduces mortality rate and sternal re-infection rate compared to conventional treatment. *Eur J Cardiothorac Surg* 2010; 38: 1, 110-113.
- 223** Sjögren, J., Malmjö, M., Gustafsson, R., Ingemansson, R. Poststernotomy mediastinitis: a review of conventional surgical treatments, vacuum-assisted closure therapy and presentation of the Lund University Hospital mediastinitis algorithm. *Eur J Cardiothorac Surg* 2006; 30: 6, 898-905.
- 224** Malmjö, M., Ingemansson, R., Sjögren, J. Mechanisms governing the effects of vacuum-assisted closure in cardiac surgery. *Plast Reconstr Surg* 2007; 120: 5, 1266-1275.
- 225** Hersh, R.E., Jack, J.M., Dahman, M.I. et al. The vacuum-assisted closure device as a bridge to sternal wound closure. *Ann Plast Surg* 2001; 46: 3, 250-254.
- 226** Gustafsson, R.I., Sjögren, J., Ingemansson, R. Deep sternal wound infection: a sternal-sparing technique with vacuum-assisted closure therapy. *Ann Thorac Surg* 2003; 76: 6, 2048-2053.
- 227** Malmjö, M., Petzina, R., Ugander, M. et al. Preventing heart injury during negative pressure wound therapy in cardiac surgery: Assessment using real-time magnetic resonance imaging. *J Thorac Cardiovasc Surg* 2009; 138: 3, 712-717.
- 228** Lindstedt, S., Ingemansson, R., Malmjö, M. A rigid barrier between the heart and sternum protects the heart and lungs against rupture during negative pressure wound therapy. *J Cardiothorac Surg* 2011; 6: 1, 90.
- 229** Ingemansson, R., Malmjö, M., Lindstedt, S. A protective device for negative-pressure therapy in patients with mediastinitis. *Ann Thorac Surg* 2013; 95: 1, 362-364.
- 230** Ingemansson, R., Malmjö, M., Lindstedt, S. The HeartShield device reduces the risk for right ventricular damage in patients with deep sternal wound infection. *Innovations (Phila)* 2014; 9: 2, 137-141.
- 231** Ingemansson, R., Malmjö, M., Lindstedt, S. The Duration of Negative Pressure Wound Therapy Can Be Reduced Using the HeartShield Device in Patients With Deep Sternal Wound Infection. *Eplasty* 2014; 14: e16.
- 232** Lindstedt, S., Hansson, J., Hlebowicz, J. The effect of negative wound pressure therapy on haemodynamics in a laparostomy wound model. *Int Wound J* 2013; 10: 3, 285-290.
- 233** Anesäter, E., Roupé, M., Robertsson, P. et al. The influence on wound contraction and fluid evacuation of a rigid disc inserted to protect exposed organs during negative pressure wound therapy. *Int Wound J* 2011; 8: 4, 393-399.
- 234** Anesäter, E., Borgquist, O., Torbrand, C. et al. A rigid disc for protection of exposed blood vessels during negative pressure wound therapy. *Surg Innov* 2013; 20: 1, 74-80.
- 235** Anesäter, E., Borgquist, O., Torbrand, C. et al. The use of a rigid disc to protect exposed structures in wounds treated with negative pressure wound therapy: effects on wound bed pressure and microvascular blood flow. *Wound Repair Regen* 2012; 20: 4, 611-616.
- 236** Upton, D., Andrews, A. Pain and trauma in negative pressure wound therapy: a review. *Int Wound J* 2015; 12: 1, 100-105.
- 237** Apostoli, A., Caula, C. [Pain and basic functional activities in a group of patients with cutaneous wounds under V.A.C. therapy in hospital setting]. [Article in Italian] *Prof Inferm* 2008; 61: 3, 158-164.

- 238** Morykwas, M. Sub-atmospheric pressure therapy: research evidence. 1st international topical negative pressure therapy ETRS Focus Group Meeting London: ETRS; 2003. p 39–44.
- 239** Fracalvieri, M., Fierro, M.T., Salomone, M. et al. Gauze-based negative pressure wound therapy: a valid method to manage pyoderma gangrenosum. *Int Wound J* 2014; 11:2, 164–168.
- 240** Rafter, L. Use of a soft silicone-based film dressing in negative pressure wound therapy. *Wounds UK* 2013; 9: 4, 107–113.
- 241** Franczyk, M., Lohman, R.F., Agarwal, J.P. et al. The impact of topical lidocaine on pain level assessment during and after vacuum-assisted closure dressing changes: a double-blind, prospective, randomized study. *Plast Reconstr Surg* 2009; 124: 3, 854–861.
- 242** Agrawal, V., Wilson, K., Reyna, R., Emran, M.A. Feasibility of 4% Topical Lidocaine for Pain Management During Negative Pressure Wound Therapy Dressing Changes in Pediatric Patients. *J Wound Ostomy Continence Nurs* 2015; 42: 6, 640–642.
- 243** Woo, K.Y. 0.2% topical lidocaine reduces pain during and immediately after vacuum-assisted closure dressing changes, but effects may be short lived. *Evid Based Nurs* 2010; 13: 1, 16–17.
- 244** Fleischmann, W., Strecker, W., Bombelli, M., Kinzi, L. [Vacuum sealing as treatment of soft tissue damage in open fractures]. [Article in German] *Unfallchirurg* 1993; 96: 9, 488–492.
- 245** Fleischmann, W., Becker, U., Bischoff, M., Hoekstra, H. Indication and operative technique in vacuum sealing. *J Bone Joint Surg Br* 1994; 98: 76–78.
- 246** Gage, M.J., Yoon, R.S., Egol, K.A., Liporace, F.A. Uses of negative pressure wound therapy in orthopedic trauma. *Orthop Clin North Am* 2015; 46: 2, 227–234.
- 247** Ali, M. [Negative pressure therapy in traumatology]. [Article in French] *Soins* 2014; 782: 35–36.
- 248** Wei, D., Wang, Y., Yuan, J. et al. [One-stage operation for pelvis and acetabular fractures combined with Morel-Lavallée injury by internal fixation associated with vacuum sealing drainage]. [Article in Chinese] *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi* 2014; 28: 1, 38–42.
- 249** Zagrocki, L., Ross, A., Hicks, A. Management of degloving injuries of the lower extremity: a case report of a forklift injury. *Foot Ankle Spec* 2013; 6: 2, 150–153.
- 250** Kakagia, D., Karadimas, E.J., Drosos, G. et al. Wound closure of leg fasciotomy: Comparison of vacuum-assisted closure versus shoelace technique. A randomised study. *Injury* 2014; 45: 5, 890–893. M
- 251** Stannard, J.P., Volgas, D.A., Stewart, R. et al. Negative pressure wound therapy after severe open fractures: a prospective randomized study. *J Orthop Trauma* 2009; 23: 8, 552–557.
- 252** Kim, Y.H., Hwang, K.T., Kim, J.T., Kim, S.W. What is the ideal interval between dressing changes during negative pressure wound therapy for open traumatic fractures? *J Wound Care* 2015; 24: 11, 536–542.
- 253** Milcheski, D.A., Ferreira, M.C., Nakamoto, H.A. et al. Subatmospheric pressure therapy in the treatment of traumatic soft tissue injuries. *Rev Col Bras Cir* 2013; 40: 5, 392–396.
- 254** Raju, A., Ooi, A., Ong, Y., Tan, B. Traumatic lower limb injury and microsurgical free flap reconstruction with the use of negative pressure wound therapy: is timing crucial? *J Reconstr Microsurg* 2014; 30: 06, 427–430.
- 255** Dong, F., Zhu, J., Li, Y., Lu, C. [Sequential therapy of vacuum sealing drainage and pedicled flap transplantation for children with motorcycle spoke heel injury]. [Article in Chinese] *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi* 2015; 29: 4, 462–466.
- 256** Wilkin, G., Khogali, S., Garbedian, S. et al. Negative-pressure wound therapy after fasciotomy reduces muscle-fiber regeneration in a pig model. *J Bone Joint Surg Am* 2014; 96: 16, 1378–1385.
- 257** Milcheski, D.A., Zampieri, F.M., Nakamoto, H.A. et al. Negative pressure wound therapy in complex trauma of perineum. *Rev Col Bras Cir* 2013; 40: 4, 312–317.
- 258** Beckett, A., Tien, H. What's new in operative trauma surgery in the last 10 years. *Curr Opin Crit Care* 2013; 19: 6, 599–604.
- 259** Anagnostakos, K., Schmitt, C. Can periprosthetic hip joint infections be successfully managed by debridement and prosthesis retention? *World J Orthop* 2014; 5: 3, 218–224.
- 260** Lehner, B., Bernd, L. [V.A.C.-instill therapy in periprosthetic infection of hip and knee arthroplasty]. [Article in German] *Zentralbl Chir* 2006; 131 Suppl 1: S160–S164.
- 261** Rispoli, D.M., Horne, B.R., Kryzak, T.J., Richardson, M.W. Description of a technique for vacuum-assisted deep drains in the management of cavity defects and deep infections in devastating military and civilian trauma. *J Trauma Inj Infect Crit Care* 2010; 68: 5, 1247–1252.
- 262** Schlatterer, D.R., Hirschfeld, A.G., Webb, L.X. Negative pressure wound therapy in grade IIIB tibial fractures: fewer infections and fewer flap procedures? *Clin Orthop Relat Res* 2015; 473: 5, 1802–1811.
- 263** Daglar, B., Ozkaya, U., Sökücü, S. et al. Use of vacuum-assisted closure in the topical treatment of surgical site infections. *Acta Orthop Traumatol Turc* 2009; 43: 4, 336–342.
- 264** Lüdemann M, Haid S, Wülker N, Rudert M. [Results of vacuum sealing therapy in joint infections]. *Z Orthop Ihre Grenzgeb* 2006 Nov-Dec; 144(6):602–608 Medline.
- 265** Petersen, K., Waterman, P. Prophylaxis and treatment of infections associated with penetrating traumatic injury. *Expert Rev Anti Infect Ther* 2011; 9: 1, 81–96.
- 266** Murray, C.K., Obremskey, W.T., Hsu, J.R. et al. Prevention of Combat-Related Infections Guidelines Panel. Prevention of infections associated with combat-related extremity injuries. *J Trauma Inj Infect Crit Care* 2011; 71: 2 Suppl 2, S235–S257.
- 267** Murray, C.K., Hsu, J.R., Solomkin, J.S. et al. Prevention and management of infections associated with combat-related extremity injuries. *J Trauma Inj Infect Crit Care* 2008; 64: 3 Supplement, S239–S251.
- 268** Hospenthal, D.R., Murray, C.K., Andersen, R.C. et al. Guidelines for the prevention of infections associated with combat-related injuries: 2011 update: endorsed by the Infectious Diseases Society of America and the Surgical Infection Society. *J Trauma* 2011; 71: 2 Suppl 2, S210–S234.
- 269** Hospenthal, D.R., Murray, C.K., Andersen, R.C. et al. Executive summary: guidelines for the prevention of infections associated with combat-related injuries: 2011 update: endorsed by the Infectious Diseases Society of America and the Surgical Infection Society. *J Trauma Inj Infect Crit Care* 2011; 71: 2 Suppl 2, S202–S209.
- 270** Lessing, M.C., James, R.B., Ingram, S.C. Comparison of the effects of different negative pressure wound therapy modes-continuous, noncontinuous, and with instillation-on porcine excisional wounds. *Eplasty* 2013; 13: e51.
- 271** Horch, R.E., Dragu, A., Lang, W. et al. Coverage of exposed bones and joints in critically ill patients: lower extremity salvage with topical negative

pressure therapy. *J Cutan Med Surg* 2008; 12: 5, 223–229.

**272** Vaseenon, T., Somsuk, W. Negative pressure wound therapy for traumatic foot and ankle wound: two case reports and review of the literature. *J Med Assoc Thai* 2015; 98: 1, 111–116.

**273** Morykwas, M.J., David, L.R., Schneider, A.M. et al. Use of subatmospheric pressure to prevent progression of partial-thickness burns in a swine model. *J Burn Care Rehabil* 1999; 20: 1 Pt 1, 15–21.

**274** Cozart, R.F., Atchison, J.R., Lett, E.D. et al. The use of controlled subatmospheric pressure to promote wound healing in preparation for split-thickness skin grafting in a fourth degree burn. *Tenn Med* 1999; 92: 10, 382–384.

**275** Chen, J., Zhou, J.J., Su, G.L. et al. [Evaluation of the clinical curative effect of applying vacuum sealing drainage therapy in treating deep partial-thickness burn wound at the initial stage]. [Article in Chinese] *Zhonghua Shao Shang Za Zhi* 2010; 2: 3, 170–174.

**276** Haslik, W., Kamolz, L.P., Andel, H. et al. [The use of subatmospheric pressure to prevent burn wound progression: first experiences in burn wound treatment]. [Article in German] *Zentralbl Chir* 2004; 129 Suppl 1: S62–S63.

**277** Liu, Y., Zhou, Q., Wang, Y. et al. Negative pressure wound therapy decreases mortality in a murine model of burn-wound sepsis involving *Pseudomonas aeruginosa* infection. *PLoS ONE* 2014; 9: 2, e90494.

**278** Dowsett, C., Davis, L., Henderson, V., Searle, R. The economic benefits of negative pressure wound therapy in community-based wound care in the NHS. *Int Wound J* 2012; 9: 5, 544–552.

**279** Banwell, P.E. Topical negative pressure wound therapy: advances in burn wound management. *Ostomy Wound Manage* 2004; 50: 11A Suppl, 9S–14S.

**280** Hop, M.J., Bloemen, M.C., van Baar, M.E. et al. Cost study of dermal substitutes and topical negative pressure in the surgical treatment of burns. *Burns* 2014; 40: 3, 388–396.

**281** Waltzman, J.T., Bell, D.E. Vacuum-assisted closure device as a split-thickness skin graft bolster in the burn population. *J Burn Care Res* 2014; 35: 5, e338–e342.

**282** Leffler, M., Horch, R.E., Dragu, A., Bach, A.D. The use of the artificial dermis (Integra®) in combination with vacuum assisted closure for reconstruction of an extensive burn scar – A case report. *J Plast Reconstr Aesthet Surg* 2010; 63: 1, e32–e35.

**283** Kamolz, L.P., Lumenta, D.B., Parvizi, D. et al. Skin graft fixation in severe burns: use of topical negative pressure. *Ann Burns Fire Disasters* 2014; 27: 3, 141–145.

**284** Petkar, K.S., Dhanraj, P., Kingsly, P.M. et al. A prospective randomized controlled trial comparing negative pressure dressing and conventional dressing methods on split-thickness skin grafts in burned patients. *Burns* 2011; 37: 6, 925–929.

**285** Bloemen, M.C., van der Wal, M.B., Verhaegen, P.D. et al. Clinical effectiveness of dermal substitution in burns by topical negative pressure: A multicenter randomized controlled trial. *Wound Repair Regen* 2012; 20: 6, 797–805.

**286** Hoeller, M., Schintler, M.V., Pfurttscheller, K. et al. A retrospective analysis of securing autologous split-thickness skin grafts with negative pressure wound therapy in paediatric burn patients. *Burns* 2014; 40: 6, 1116–1120.

**287** Schiestl, C., Meuli, M., Trop, M., Neuhaus, K. Management of burn wounds. *Eur J Pediatr Surg* 2013; 23: 05, 341–348.

**288** Acosta, S., Monsen, C., Dencker, M. Clinical outcome and microvascular blood flow in VAC® - and Sorbalgon® -treated peri-vascular infected wounds in the groin after vascular surgery - an early interim analysis. *Int Wound J* 2013; 10: 4, 377–382.

**289** Danks, R.R., Lairet, K. Innovations in caring for a large burn in the Iraq war zone. *J Burn Care Res* 2010; 31: 4, 665–669.

**290** Chong, S.J., Liang, W.H., Tan, B.K. Use of multiple VAC devices in the management of extensive burns: The total body wrap concept. *Burns* 2010; 36: 7, e127–e129.

**291** Hardin, M.O., Mace, J.E., Ritchie, J.D. et al. An experience in the management of the open abdomen in severely injured burn patients. *J Burn Care Res* 2012; 33: 4, 491–496.

**292** Gümüş N. Negative pressure dressing combined with a traditional approach for the treatment of skull burn. *Niger J Clin Pract* 2012; 15: 4, 494–497.

**293** Horch, R.E. [Changing paradigms in reconstructive surgery by vacuum therapy?]. [Article in German] *Zentralbl Chir* 2006; 131 Suppl 1: S44–S49.

**294** Janis, J.E., Kwon, R.K., Attinger, C.E. The new reconstructive ladder: modifications to the traditional model. *Plast Reconstr Surg* 2011; 127: Suppl 1, 205S–212S.

**295** Polykandriotis, E., Schmidt, V.J., Kneser, U. et al. [Bioreactors in regenerative medicine from a technical device to a reconstructive alternative?]. [Article in German] *Handchir Mikrochir Plast Chir* 2012; 44: 4, 198–203.

**296** Benech, A., Arcuri, F., Pogliano, G. et al. Vacuum-assisted closure therapy in reconstructive surgery. *Acta Otorhinolaryngol Ital* 2012; 32: 3, 192–197.

**297** Fleming, M.E., ODaniel, A., Bharmal, H., Valerio, I. Application of the orthoplastic reconstructive ladder to preserve lower extremity amputation length. *Ann Plast Surg* 2014; 73: 2, 183–189.

**298** Kakagia, D., Karadimas, E., Drosos, G. et al. Vacuum-assisted closure downgrades reconstructive demands in high-risk patients with severe lower extremity injuries. *Acta Chir Plast* 2009; 51: 3–4, 59–64.

**299** Maurya, S., Mukherjee, M.K., Bhandari, P.S. Reconstructive challenges in war wounds. *Indian Journal of Plastic Surgery* 2012; 45: 2, 332–339.

**300** Kneser, U., Bach, A.D., Polykandriotis, E. et al. Delayed reverse sural flap for staged reconstruction of the foot and lower leg. *Plast Reconstr Surg* 2005; 116: 7, 1910–1917.

**301** Blume, P.A., Key, J.J., Thakor, P. et al. Retrospective evaluation of clinical outcomes in subjects with split-thickness skin graft: comparing V.A.C.® therapy and conventional therapy in foot and ankle reconstructive surgeries. *Int Wound J* 2010; 7: 6, 480–487.

**302** Stiefel, D., Schiestl, C.M., Meuli, M. The positive effect of negative pressure: vacuum-assisted fixation of Integra artificial skin for reconstructive surgery. *J Pediatr Surg* 2009; 44: 3, 575–580.

**303** Jeschke, M.G., Rose, C., Angele, P. et al. Development of new reconstructive techniques: use of Integra in combination with fibrin glue and negative-pressure therapy for reconstruction of acute and chronic wounds. *Plast Reconstr Surg* 2004; 113: 2, 525–530.

**304** Chio, E.G., Agrawal, A. A randomized, prospective, controlled study of forearm donor site healing when using a vacuum dressing. *Otolaryngol Head Neck Surg* 2010; 142: 2, 174–178.

**305** Moisidis, E., Heath, T., Boorer, C., et al. A prospective, blinded, randomized, controlled clinical trial of topical negative pressure use in skin grafting. *Plast Reconstr Surg* 2004; 114: 4, 917–922.

- 306** Llanos, S., Danilla, S., Barraza, C. et al. Effectiveness of negative pressure closure in the integration of split thickness skin grafts: a randomized, double-masked, controlled trial. *Ann Surg* 2006; 244: 5, 700–705.
- 307** Liao, Q., Xu, J., Weng, X.J. et al. [Effectiveness of vacuum sealing drainage combined with anti-taken skin graft for primary closing of open amputation wound]. [Article in Chinese] *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi* 2012; 26: 5, 558–562.
- 308** Wittmann, D.H., Iskander, G.A. The compartment syndrome of the abdominal cavity: a state of the art review. *J Intensive Care Med* 2000; 15: 4, 201–220.
- 309** Ertel, W., Oberholzer, A., Platz, A. et al. Incidence and clinical pattern of the abdominal compartment syndrome after damage-control laparotomy in 311 patients with severe abdominal and/or pelvic trauma. *Crit Care Med* 2000; 28: 6, 1747–1753.
- 310** Shapiro, M.B., Jenkins, D.H., Schwab, C.W., Rotondo, M.F. Damage control: collective review. *J Trauma* 2000; 49: 5, 969–978.
- 311** Aprahamian, C., Wittmann, D.H., Bergstein, J.M., Quebbeman, E.J. Temporary abdominal closure (TAC) for planned relaparotomy (etappenlavage) in trauma. *J Trauma Inj Infect Crit Care* 1990; 30: 6, 719–723.
- 312** Garcia-Sabrido, J.L., Tallado, J.M. et al. Treatment of severe intra-abdominal sepsis and/or necrotic foci by an open-abdomen approach. Zipper and zipper-mesh techniques. *Arch Surg* 1988; 123: 2, 152–156.
- 313** Morris, J.A. Jr., Eddy, V.A., Blinman, T.A. et al. The staged celiotomy for trauma. Issues in unpacking and reconstruction. *Ann Surg* 1993; 217: 5, 576–586.
- 314** Graham, D.J., Stevenson, J.T., McHenry, C.R. et al. The association of intra-abdominal infection and abdominal wound dehiscence. *Am Surg* 1998; 64: 7, 660–665.
- 315** Howdieshell, T.R., Yeh, K.A., Hawkins, M.L., Cué, J.I. Temporary abdominal wall closure in trauma patients: indications, technique, and results. *World J Surg* 1995; 19: 1, 154–158.
- 316** Schein, M., Saadia, R., Jamieson, J.R., Decker, G.A. The sandwich technique in the management of the open abdomen. *Br J Surg* 1986; 73: 5, 369–370.
- 317** Bruhin, A., Ferreira, F., Chariker, M. et al. Systematic review and evidence based recommendations for the use of Negative Pressure Wound Therapy in the open abdomen. *Int J Surg* 2014; 12: 10, 1105–1114.
- 318** Long, K.L., Hamilton, D.A., Davenport, D.L. et al. A prospective, controlled evaluation of the abdominal reapproximation anchor abdominal wall closure system in combination with VAC therapy compared with VAC alone in the management of an open abdomen. *Am Surg* 2014; 80: 6, 567–571.
- 319** Atema, J.J., Gans, S.L., Boermeester, M.A. Systematic review and meta-analysis of the open abdomen and temporary abdominal closure techniques in non-trauma patients. *World J Surg* 2015; 39: 4, 912–925.
- 320** Rausei, S., Amico, F., Frattini, F. et al. A Review on Vacuum-assisted Closure Therapy for Septic Peritonitis Open Abdomen Management. *Surg Technol Int* 2014; 25: 68–72.
- 321** Rencüzogulları, A., Dalci, K., Eray, I.C. et al. Comparison of early surgical alternatives in the management of open abdomen: a randomized controlled study. *Ulus Trauma Acil Cerrahi Derg* 2015; 21: 3, 168–174.
- 322** Aboutanos, S.Z., Aboutanos, M.B., Malhotra, A.K. et al. Management of a pregnant patient with an open abdomen. *J Trauma Inj Infect Crit Care* 2005; 59: 5, 1052–1056.
- 323** Barker, D.E., Kaufman, H.J., Smith, L.A. et al. Vacuum pack technique of temporary abdominal closure: a 7-year experience with 112 patients. *J Trauma Inj Infect Crit Care* 2000; 48: 2, 201–207.
- 324** Brock, W.B., Barker, D.E., Burns, R.P. Temporary closure of open abdominal wounds: the vacuum pack. *Am Surg* 1995; 61: 1, 30–35.
- 325** Garner, G.B., Ware, D.N., Cocanour, C.S. et al. Vacuum-assisted wound closure provides early fascial reapproximation in trauma patients with open abdomens. *Am J Surg* 2001; 182: 6, 630–638.
- 326** Heller, L., Levin, S.L., Butler, C.E. Management of abdominal wound dehiscence using vacuum assisted closure in patients with compromised healing. *Am J Surg* 2006; 191: 2, 165–172.
- 327** Hinck, D., Struve, R., Gatzka, F., Schürmann, G. [Vacuum-assisted fascial closure in the management of diffuse peritonitis]. [Article in German] *Zentralbl Chir* 2006; 131 Suppl 1: S108–S110.
- 328** Kaplan, M. Negative pressure wound therapy in the management of abdominal compartment syndrome. *Ostomy Wound Manage* 2004; 50: 1A Suppl, 20S–25S.
- 329** Kaplan, M. Abdominal compartment syndrome. *Ostomy Wound Manage* 2004; 50: 4A Suppl, 20–21 I.
- 330** Kaplan, M. Managing the open abdomen. *Ostomy Wound Manage* 2004; 50: 1A Suppl, C2, 1–18.
- 331** Markley, M.A., Mantor, P.C., Letton, R.W., Tuggle, D.W. Pediatric vacuum packing wound closure for damage-control laparotomy. *J Pediatr Surg* 2002; 37: 3, 512–514.
- 332** Miller, P.R., Meredith, J.W., Johnson, J.C., Chang, M.C. Prospective evaluation of vacuum-assisted fascial closure after open abdomen: planned ventral hernia rate is substantially reduced. *Ann Surg* 2004; 239: 5, 608–616.
- 333** Miller, P.R., Thompson, J.T., Faler, B.J. et al. Late fascial closure in lieu of ventral hernia: the next step in open abdomen management. *J Trauma Inj Infect Crit Care* 2002; 53: 5, 843–849.
- 334** Penn, E., Rayment, S. Management of a dehisced abdominal wound with VAC therapy. *Br J Nurs* 2004; 13: 4, 194–201.
- 335** Quah, H.M., Maw, A., Young, T., Hay, D.J. Vacuum-assisted closure in the management of the open abdomen: a report of a case and initial experiences. *J Tissue Viability* 2004; 14: 2, 59–62.
- 336** Sauter, E.R. Temporary closure of open abdominal wounds by the modified sandwich-vacuum pack technique. (*Br J Surg* 2003; 90: 718722). *Br J Surg* 2003; 90: 8, 1021–1022.
- 337** Scott, B.G., Feanny, M.A., Hirshberg, A. Early definitive closure of the open abdomen: a quiet revolution. *Scand J Surg* 2005; 94: 1, 9–14.
- 338** Steenvoorde, P., van Engeland, A., Bonsing, B. et al. Combining topical negative pressure and a Bogota bag for managing a difficult laparotomy. *J Wound Care* 2004; 13: 4142–143.
- 339** Stone, P.A., Hass, S.M., Flaherty, S.K. et al. Vacuum-assisted fascial closure for patients with abdominal trauma. *J Trauma Inj Infect Crit Care* 2004; 57: 5, 1082–1086.
- 340** Stonerock, C.E., Bynoe, R.P., Yost, M.J., Nottingham, J.M. Use of a vacuum-assisted device to facilitate abdominal closure. *Am Surg* 2003; 69: 12, 1030–1034.
- 341** Suliburk, J.W., Ware, D.N., Balogh, Z., McKinley, B.A. et al. Vacuum-assisted wound closure achieves early fascial closure of open abdomens after severe trauma. *J Trauma Inj Infect Crit Care* 2003; 55: 6, 1155–1160.
- 342** Swan, M.C., Banwell, P.E. The open abdomen: aetiology, classification and

current management strategies. *J Wound Care* 2005; 14: 1,7–11.

**343** Wild, T., Stortecy, S., Stremitzer, S. et al. [Abdominal dressing a new standard in therapy of the open abdomen following secondary peritonitis?]. [Article in German] *Zentralbl Chir* 2006; 131 Suppl 1: S111–S114.

**344** Wild, T., Stremitzer, S., Budzanowski, A. et al. [Abdominal dressing - a new method of treatment for open abdomen following secondary peritonitis]. [Article in German] *Zentralbl Chir* 2004; 129 Suppl 1: S20–S23.

**345** Stonerock, C.E., Bynoe, R.P., Yost, M.J., Nottingham, J.M. Use of a vacuum-assisted device to facilitate abdominal closure. *Am Surg* 2003; 69: 12, 1030–1034.

**346** Garner, G.B., Ware, D.N., Cocanour, C.S. et al. Vacuum-assisted wound closure provides early fascial reapproximation in trauma patients with open abdomens. *Am J Surg* 2001; 182: 6, 630–638.

**347** Carlson, G.L., Patrick, H., Amin, A.I. et al. Management of the open abdomen: a national study of clinical outcome and safety of negative pressure wound therapy. *Ann Surg* 2013; 257: 6, 1154–1159.

**348** Richter, S., Dold, S., Doberauer, J.P. et al. Negative pressure wound therapy for the treatment of the open abdomen and incidence of enteric fistulas: a retrospective bicentre analysis. *Gastroenterol Res Pract* 2013; 2013: 730829.

**349** Fieger, A.J., Schwatlo, F., Mündel, D.F. et al. [Abdominal vacuum therapy for the open abdomen - a retrospective analysis of 82 consecutive patients]. [Article in German] *Zentralbl Chir* 2011; 136: 1, 56–60.

**350** Hougaard, H.T., Ellebaek, M., Holst, U.T., Qvist, N. The open abdomen: temporary closure with a modified negative pressure therapy technique. *Int Wound J* 2014; 11: s1 Suppl 1, 13–16.

**351** Mutafchyski, V.M., Popivanov, G.I., Kjossev, K.T., Chipeva, S. Open abdomen and VAC® in severe diffuse peritonitis. *J R Army Med Corps* 2016; 162: 1, 30–34.

**352** Rasilainen, S.K., Mentula, P.J., Leppäniemi, A.K. Vacuum and mesh-mediated fascial traction for primary closure of the open abdomen in critically ill surgical patients. *Br J Surg* 2012; 99: 12, 1725–1732.

**353** Bjarnason, T., Montgomery, A., Acosta, S., Petersson, U. Evaluation of the open abdomen classification system: a validity and reliability analysis. *World J Surg* 2014; 38: 12, 3112–3124.

**354** Rasilainen, S.K., Juhani, M.P., Kalevi, L.A. Microbial colonization of open abdomen in critically ill surgical patients. *World J Emerg Surg* 2015; 10: 1, 25.

**355** Jannasch, O., Tautenhahn, J., Lippert, H., Meyer, F. [Temporary abdominal closure and early and late pathophysiological consequences of treating an open abdomen]. [Article in German] *Zentralbl Chir* 2011; 136: 6, 575–584.

**356** Willms, A., Güsgen, C., Schaaf, S. et al. Management of the open abdomen using vacuum-assisted wound closure and mesh-mediated fascial traction. *Langenbecks Arch Surg* 2015; 400: 1, 91–99.

**357** Fortelny, R.H., Hofmann, A., Gruber-Blum, S. et al. Delayed closure of open abdomen in septic patients is facilitated by combined negative pressure wound therapy and dynamic fascial suture. *Surg Endosc* 2014; 28: 3, 735–740.

**358** Mukhi, A., Minor, S. Management of the open abdomen using combination therapy with ABRA and ABThera systems. *Can J Surg* 2014; 57: 5, 314–319.

**359** Salman, A.E., Yetisir, F., Aksoy, M. et al. Use of dynamic wound closure system in conjunction with vacuum-assisted closure therapy in delayed closure of open abdomen. *Hernia* 2014; 18: 1, 99–104.

**360** Yanar, H., Sivriköz, E. Management of open abdomen: single center

experience. *Gastroenterol Res Pract* 2013; 2013: 584378.

**361** Szymt, K., Łukasz, K., Bobkiewicz, A. et al. Comparison of the effectiveness of the treatment using standard methods and negative pressure wound therapy (NPWT) in patients treated with open abdomen technique. *Pol Przegl Chir* 2015; 87: 1, 22–30.

**362** Hutan, J.M., Hutan, M.S., Skultety, J. et al. Use of intraabdominal VAC (Vacuum Assisted Closure) lowers mortality and morbidity in patients with open abdomen. *Bratisl Lek Listy* 2013; 114: 8, 451–454.

**363** Gutierrez, I.M., Gollin, G. Negative pressure wound therapy for children with an open abdomen. *Langenbecks Arch Surg* 2012; 397: 8, 1353–1357.

**364** DHondt, M., DHaeninck, A., Dedrye, L. et al. Can vacuum-assisted closure and instillation therapy (VAC-Instill® therapy) play a role in the treatment of the infected open abdomen? *Tech Coloproctol* 2011; 15: 1, 75–77.

**365** Lindstedt, S., Malmjö, M., Hlebowicz, J., Ingemansson, R. Comparative study of the microvascular blood flow in the intestinal wall, wound contraction and fluid evacuation during negative pressure wound therapy in laparotomy using the V.A.C. abdominal dressing and the ABThera open abdomen negative pressure therapy. *Int Wound J* 2015; 12: 1, 83–88.

**366** Gillespie, B.M., Rickard, C.M., Thalib, L. et al. Use of Negative-Pressure Wound Dressings to Prevent Surgical Site Complications After Primary Hip Arthroplasty. *Surg Innov* 2015; 22: 5, 488–495.

**367** Fu, R.H., Weinstein, A.L., Chang, M.M. et al. Risk factors of infected sternal wounds versus sterile wound dehiscence. *J Surg Res* 2016; 200: 1, 400–407.

**368** Gatti, G., Dell'Angela, L., Barbati, G. et al. A predictive scoring system for deep sternal wound infection after bilateral internal thoracic artery grafting. *Eur J Cardiothorac Surg* 2016; 49: 3, 910–917.

**369** Lemaignan, A., Birgand, G., Ghodhbane, W. et al. Sternal wound infection after cardiac surgery: incidence and risk factors according to clinical presentation. *Clin Microbiol Infect* 2015; 21: 7, 674 e11–e18.

**370** Guy, H., Grothier, L. Using negative pressure therapy in wound healing. *Nurs Times* 2012; 108: 36, 16–20.

**371** Henderson, V., Timmons, J., Hurd, T., Deroo, K., Maloney, S., Sabo, S. NPWT in everyday practice Made Easy. *Wound Int* 2010; 1: 5.

**372** Howell, R.D., Hadley, S., Strauss, E., Pelham, F.R. Blister formation with negative pressure dressings after total knee arthroplasty. *Curr Orthop Pract* 2011; 22: 2, 176–179.

**373** Sjögren, J., Gustafsson, R., Nilsson, J. et al. Clinical outcome after poststernotomy mediastinitis: vacuum-assisted closure versus conventional treatment. *Ann Thorac Surg* 2005; 79: 6, 2049–2055.

**374** Sjögren, J., Nilsson, J., Gustafsson, R. et al. The impact of vacuum-assisted closure on long-term survival after post-sternotomy mediastinitis. *Ann Thorac Surg* 2005; 80: 4, 1270–1275.

**375** Doss, M., Martens, S., Wood, J.P. et al. Vacuum-assisted suction drainage versus conventional treatment in the management of poststernotomy osteomyelitis. *Eur J Cardiothorac Surg* 2002; 22: 6, 934–938.

**376** Mokhtari, A., Sjögren, J., Nilsson, J. et al. The cost of vacuum-assisted closure therapy in treatment of deep sternal wound infection. *Scand Cardiovasc J* 2008; 42: 1, 85–89.

**377** Debreceni, T., Szeráfin, T., Galajda, Z. et al. [Results of vacuum-assisted wound closure system in the treatment of sternotomy wound infections following cardiac surgery]. [Article in Hungarian] *Magy Seb* 2008; 61 Suppl: 29–35.



- 378** Tarzia, V., Carrozzini, M., Bortolussi, G. et al. Impact of vacuum-assisted closure therapy on outcomes of sternal wound dehiscence. *Interact Cardiovasc Thorac Surg* 2014; 19: 1, 70–75.
- 379** Witt-Majchrzak, A., Zelazny P., Snarska, J. Preliminary outcome of treatment of postoperative primarily closed sternotomy wounds treated using negative pressure wound therapy. *Pol Przegl Chir* 2015; 86: 10, 456–465.
- 380** Atkins, B.Z., Wooten, M.K., Kistler, J. et al. Does negative pressure wound therapy have a role in preventing poststernotomy wound complications? *Surg Innov* 2009; 16: 2, 140–146.
- 381** Atkins, B.Z., Tetterton, J.K., Petersen, R.P. et al. Laser Doppler flowmetry assessment of peristernal perfusion after cardiac surgery: beneficial effect of negative pressure therapy. *Int Wound J* 2011; 8: 1, 56–62.
- 382** Colli, A., Camara, M.L. First experience with a new negative pressure incision management system on surgical incisions after cardiac surgery in high risk patients. *J Cardiothorac Surg* 2011; 6: 1, 160.
- 383** Grauhan, O., Navasardyan, A., Hofmann, M. et al. Prevention of poststernotomy wound infections in obese patients by negative pressure wound therapy. *J Thorac Cardiovasc Surg* 2013; 145: 5, 1387–1392.
- 384** Hopkins, S.P., Kazmers, A. Management of vascular infections in the groin. *Ann Vasc Surg* 2000; 14: 5, 532–539.
- 385** Argenta, P.A., Rahaman, J., Gretz, H.F. 3rd. et al. Vacuum-assisted closure in the treatment of complex gynecologic wound failures. *Obstet Gynecol* 2002; 99: 3, 497–501.
- 386** Kent, K.C., Bartek, S., Kuntz, K.M. et al. Prospective study of wound complications in continuous infrainguinal incisions after lower limb arterial reconstruction: Incidence, risk factors, and cost. *Surgery* 1996; 119: 4, 378–383.
- 387** Meyer, T., Schweiger, H., Lang, W. Extraanatomic bypass in the treatment of prosthetic vascular graft infection manifesting in the groin. *Vasa* 1999; 28: 4, 283–288.
- 388** Castier, Y., Francis, F., Cerceau, P. et al. Cryopreserved arterial allograft reconstruction for peripheral graft infection. *J Vasc Surg* 2005; 41: 1, 30–37.
- 389** Collier, M. Topical negative pressure therapy. *Nurs Times* 2003; 99: 5, 54–55.
- 390** Colwell, A.S., Donaldson, M.C., Belkin, M., Orgill, D.P. Management of early groin vascular bypass graft infections with sartorius and rectus femoris flaps. *Ann Plast Surg* 2004; 52: 1, 49–53.
- 391** Demaria, R., Giovannini, U.M., Téot, L., Chaptal, P.A. Using VAC to treat a vascular bypass site infection. *J Wound Care* 2001; 10: 2, 12–13.
- 392** Dosluoglu, H.H., Schimpf, D.K., Schultz, R., Cherr, G.S. Preservation of infected and exposed vascular grafts using vacuum assisted closure without muscle flap coverage. *J Vasc Surg* 2005; 42: 5, 989–992.
- 393** Giovannini, U.M., Demaria, R.G., Chaptal, P.A., Téot, L. Negative pressure for the management of an exposed vascular dacron polyester patch. *Ann Plast Surg* 2001; 47: 5, 577–578.
- 394** Heller, G., Savolainen, H., Widmer, M.K. et al. [Vacuum-assisted therapy in vascular surgery]. [Article in German] *Zentralbl Chir* 2004; 129 Suppl 1: S66–S70.
- 395** Monsen, C., Acosta, S., Mani, K., Wann-Hansson, C. A randomised study of NPWT closure versus alginate dressings in peri-vascular groin infections: quality of life, pain and cost. *J Wound Care* 2015; 24: 6, 252–206.
- 396** Monsen, C., Wann-Hansson, C., Victorsson, C., Acosta, S. Vacuum-assisted wound closure versus alginate for the treatment of deep perivascular wound infections in the groin after vascular surgery. *J Vasc Surg* 2014; 59: 1, 145–151.
- 397** Heller, G., Savolainen, H., Dick, F. et al. V.A.C.-standards in vascular surgery. *J Wound Healing* 2005; S1: 18–20.
- 398** Lang, W., Horch, R.E. [Distal extremity reconstruction for limb salvage in diabetic foot ulcers with pedal bypass, flap plasty and vacuum therapy]. [Article in German] *Zentralbl Chir* 2006; 131: Suppl 1, S146–S150.
- 399** Berger, P., de Bie, D., Moll, F.L., de Borst, G.J. Negative pressure wound therapy on exposed prosthetic vascular grafts in the groin. *J Vasc Surg* 2012; 56: 3, 714–720.
- 400** Mayer, D., Hasse, B., Koelliker, J. et al. Long-term results of vascular graft and artery preserving treatment with negative pressure wound therapy in Szilagyi grade III infections justify a paradigm shift. *Ann Surg* 2011; 254: 5, 754–760.
- 401** Verma, H., Ktenidis, K., George, R.K., Tripathi, R. Vacuum-assisted closure therapy for vascular graft infection (Szilagyi grade III) in the groin—a 10-year multi-center experience. *Int Wound J* 2015; 12: 3, 317–321.
- 402** Kotsis, T., Lioupis, C. Use of vacuum assisted closure in vascular graft infection confined to the groin. *Acta Chir Belg* 2007; 107: 1, 37–44.
- 403** Matatov, T., Reddy, K.N., Doucet, L.D. et al. Experience with a new negative pressure incision management system in prevention of groin wound infection in vascular surgery patients. *J Vasc Surg* 2013; 57: 3, 791–795.
- 404** Dosluoglu, H.H., Loghmanee, C., Lall, P. et al. Management of early (<30 day) vascular groin infections using vacuum-assisted closure alone without muscle flap coverage in a consecutive patient series. *J Vasc Surg* 2010; 51: 5, 1160–1166.
- 405** Hamed, O., Muck, P.E., Smith, J.M. et al. Use of vacuum-assisted closure (VAC) therapy in treating lymphatic complications after vascular procedures: new approach for lymphoceles. *J Vasc Surg* 2008; 48: 6, 1520–1523, 3, e1–4.
- 406** Greer, S.E., Adelman, M., Kasabian, A. et al. The use of subatmospheric pressure dressing therapy to close lymphocutaneous fistulas of the groin. *Br J Plast Surg* 2000; 53: 6, 484–487.
- 407** Ito, H., Arai, M., Ishigaki, H. et al. [The use of negative pressure wound therapy to treat wound necrosis and groin lymphorrhea after inguinal lymph nodes dissection: a case report]. [Article in Japanese] *Nihon Hinyokika Gakkai Zasshi* 2012; 103: 1, 22–26. Medline doi:10.5980/jpnjuro.103.22
- 408** Lemaire, V., Brilmaker, J., Kerzmann, A., Jacquemin, D. Treatment of a groin lymphatic fistula with negative pressure wound therapy. *Eur J Vasc Endovasc Surg* 2008; 36: 4, 449–451.
- 409** Rau, O., Reiher, F., Tautenhahn, J., Allhoff, E.P. [V.A.C. (Vacuum Assisted Closure) therapy as a treatment option in complications following lymphadenectomy in patients with penile cancer]. [Article in German] *Zentralbl Chir* 2006; 131 Suppl 1: S153–S156.
- 410** Steenvoorde, P., Slotema, E., Adhin, S., Oskam, J. Deep infection after ilioinguinal node dissection: vacuum-assisted closure therapy? *Int J Low Extrem Wounds* 2004; 3: 4, 223–226.
- 411** Eginton, M.T., Brown, K.R., Seabrook, G.R. et al. A prospective randomized evaluation of negative-pressure wound dressings for diabetic foot wounds. *Ann Vasc Surg* 2003; 17: 6, 645–649.
- 412** Callam, M.J., Harper, D.R., Dale, J.J., Ruckley, C.V. Chronic ulcer of the leg: clinical history. *BMJ* 1987; 294: 6584, 1389–1391.
- 413** Johnson, M. The prevalence of leg ulcers in older people: implications for community nursing. *Public Health Nurs* 1995; 12: 4, 269–275.

- 414** Ashby, R.L., Gabe, R., Ali, S. et al. Clinical and cost-effectiveness of compression hosiery versus compression bandages in treatment of venous leg ulcers (Venous leg Ulcer Study IV, VenUS IV): a randomised controlled trial. *Lancet* 2014; 383: 9920, 871–879.
- 415** Coleridge Smith, P.D., Thomas P, Scurr J, Dormandy J. Causes of venous ulceration: a new hypothesis. *Br Med J (Clin Res Ed)* 1988; 296: 6638, 1726–1727.
- 416** Ghauri, A.S., Nyamekye, I.K. Leg ulceration: the importance of treating the underlying pathophysiology. *Phlebology* 2010; 25: suppl 1, 42–51.
- 417** O'Meara, S., Cullum, N., Nelson, E.A., Dumville, J.C. Compression for venous leg ulcers. *Cochrane Database Syst Rev* 2012; 11: CD000265.
- 418** Woo, K., Alavi, A., Evans, R., et al. New advances in compression therapy for venous leg ulcers. *Surg Technol Int* 2013; 23: 61–68.
- 419** Jull, A.B., Waters, J., Arnoll, B. Pentoxifylline for treating venous leg ulcers. *Cochrane Database Syst Rev* 2007; Jul 18: 3, CD001733.
- 420** Margolis, D.J., Allen-Taylor, L., Hoffstad, O., Berlin, J.A. The accuracy of venous leg ulcer prognostic models in a wound care system. *Wound Repair Regen* 2004; 12: 2, 163–168.
- 421** Dumville, J.C., Land, L., Evans, D., Peinemann, F. Negative pressure wound therapy for treating leg ulcers. *Cochrane Database Syst Rev* 2015; 7: 7, CD011354.
- 422** Vuerstaek, J.D., Vainas, T., Wuite, J. et al. State-of-the-art treatment of chronic leg ulcers: A randomized controlled trial comparing vacuum-assisted closure (V.A.C.) with modern wound dressings. *J Vasc Surg* 2006; 44: 5, 1029–1037.
- 423** Vanderwee, K., Clark, M., Deale, C. et al. Pressure ulcer prevalence in Europe: a pilot study. *J Eval Clin Pract* 2007; 13: 2, 227–235.
- 424** Power, M., Fogarty, M., Harrison, A. et al. (2015) National data report 2014-15. <https://tinyurl.com/gptku3k> (accessed 1 March 2017).
- 425** Essex, H.N., Clark, M., Sims, J. et al. Health-related quality of life in hospital inpatients with pressure ulceration: Assessment using generic health-related quality of life measures. *Wound Repair Regen* 2009; 17: 6, 797–805.
- 426** Allman, R.M. Pressure ulcer prevalence, incidence, risk factors, and impact. *Clin Geriatr Med* 1997; 13: 3, 421–436.
- 427** Berlowitz, D.R., Brandeis, G.H., Anderson, J., Brand, H.K. Predictors of pressure ulcer healing among long-term care residents. *J Am Geriatr Soc* 1997; 45: 1, 30–34.
- 428** Donini, L.M., De Felice, M.R., Tagliaccola, A. et al. Nutritional status and evolution of pressure sores in geriatric patients. *J Nutr Health Aging* 2005; 9: 6, 446–454.
- 429** Gefen, A. Tissue changes in patients following spinal cord injury and implications for wheelchair cushions and tissue loading: a literature review. *Ostomy Wound Manage* 2014; 60: 2, 34–45.
- 430** National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel and Pan Pacific Pressure Injury Alliance. Emily Haesler (ed). *Prevention and Treatment of Pressure Ulcers: Quick Reference Guide*. Cambridge Media, 2014. Perth, Australia.
- 431** de Laat, E.H., van den Boogaard, M.H., Spauwen, P.H. et al. Faster wound healing with topical negative pressure therapy in difficult-to-heal wounds: a prospective randomized controlled trial. *Ann Plast Surg* 2011; 67: 6, 626–631.
- 432** Ashby, R.L., Dumville, J.C., Soares, M.O. et al. A pilot randomised controlled trial of negative pressure wound therapy to treat grade III/IV pressure ulcers [ISRCTN69032034] [ISRCTN69032034]. *Trials* 2012; 13: 1, 119.
- 433** Ford, C.N., Reinhard, E.R., Yeh, D. et al. Interim analysis of a prospective, randomized trial of vacuum-assisted closure versus the healthpoint system in the management of pressure ulcers [discussion]. *Ann Plast Surg* 2002; 49: 1, 55–61.
- 434** Niezgodna, J. A comparison of vacuum assisted closure therapy to moist wound care in the treatment of pressure ulcers: preliminary results of a multicenter trial. 2nd World Union of Wound Healing Societies' Meeting; Paris 2004.
- 435** Bakker, K., Apelqvist, J., Lipsky, B. et al. The 2015 IWGDF guidance documents on prevention and management of foot problems in diabetes: development of an evidence-based global consensus. *Diabetes Metab Res Rev* 2016; 32: Suppl 1, 2–6.
- 436** Shaw, J.E., Sicree, R.A., Zimmet, P.Z. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010; 87: 1, 4–14.
- 437** Reiber, G.E. The epidemiology of diabetic foot problems. *Diabet Med* 1996; 13: Suppl 1, S6–S11.
- 438** Wrobel, J.S., Mayfield, J.A., Reiber, G.E. Geographic variation of lower-extremity major amputation in individuals with and without diabetes in the Medicare population. *Diabetes Care* 2001; 24: 5, 860–864.
- 439** Armstrong, D.G., Wrobel, J., Robbins, J.M. Guest Editorial: are diabetes-related wounds and amputations worse than cancer? *Int Wound J* 2007; 4: 4, 286–287.
- 440** Apelqvist, J., Bakker, K., van Houtum, W.H. et al. International consensus and practical guidelines on the management and the prevention of the diabetic foot. *Diabetes Metab Res Rev* 2000; 16: S1 Suppl 1, S84–S92.
- 441** Margolis, D.J., Kantor, J., Berlin, J.A. Healing of diabetic neuropathic foot ulcers receiving standard treatment. A meta-analysis. *Diabetes Care* 1999; 22: 5, 692–695.
- 442** Dorresteyn, J.A., Kriegsman, D.M., Valk, G.D. Complex interventions for preventing diabetic foot ulceration. *Cochrane Database Syst Rev* 2010; 1, CD007610.
- 443** Game, F.L., Hinchliffe, R.J., Apelqvist, J. et al. A systematic review of interventions to enhance the healing of chronic ulcers of the foot in diabetes. *Diabetes Metab Res Rev* 2012; 28: Suppl 1, 119–141.
- 444** Kerr, M. (2012) Foot care for people with diabetes: the economic case for change. <https://tinyurl.com/zpaf793> (accessed 1 March 2017).
- 445** Armstrong, D.G., Attinger, C.E., Boulton, A.J. et al. Guidelines regarding negative wound therapy (NPWT) in the diabetic foot. *Ostomy Wound Manage* 2004; 50: 4B Suppl, 3S–27S.
- 446** Mody, G.N., Nirmal, I.A., Duraisamy, S., Perakath, B. A blinded, prospective, randomized controlled trial of topical negative pressure wound closure in India. *Ostomy Wound Manage* 2008; 54: 12, 36–46.
- 447** Karatepe, O., Eken, I., Acet, E. et al. Vacuum assisted closure improves the quality of life in patients with diabetic foot. *Acta Chir Belg* 2011; 111: 5, 298–302.
- 448** Novinscak, T., Zvorc, M., Trojko, S. et al. [Comparison of cost-benefit of the three methods of diabetic ulcer treatment: dry, moist and negative pressure]. *Acta Med Croatica* 2010; 64: Suppl 1, 113–115.
- 449** Nordmeyer, M., Pauser, J., Biber, R. et al. Negative pressure wound

therapy for seroma prevention and surgical incision treatment in spinal fracture care. *Int Wound J* 2016; 13: 6, 1176–1179.

**450** Adogwa, O., Fatemi, P., Perez, E. et al. Negative pressure wound therapy reduces incidence of postoperative wound infection and dehiscence after long-segment thoracolumbar spinal fusion: a single institutional experience. *Spine J* 2014; 14: 12, 2911–2917.

**451** Wild, T. [Consensus of the German and Austrian societies for wound healing and wound management on vacuum closure and the VAC treatment unit]. [Article in German] *MMW Fortschr Med* 2003; 145: Suppl 3, 97–101.

**452** Wild, T., Otto, F., Mojarrad, L., Kellner, M., Götzinger, P. [Vacuum therapy basics, indication, contraindication and cost listing]. [Article in German] *Ther Umsch* 2007; 64: 9, 495–503.

**453** White, R.A., Miki, R.A., Kazmier, P., Anglen, J.O. Vacuum-assisted closure complicated by erosion and hemorrhage of the anterior tibial artery. *J Orthop Trauma* 2005; 19: 1, 56–59.

**454** Savolainen, H., Widmer, M.K., Heller, G. et al. The problematic inguinal wound in vascular surgery—what is the optimal treatment? *Int J Angiol* 2004; 13: 4, 193–196.

**455** Heller, G., Savolainen, H., Widmer, M.K. et al. [Vacuum-assisted therapy in vascular surgery]. [Article in German] *Zentralbl Chir* 2004; 129: Suppl 1, S66–S70.

**456** Karl, T., Modic, P.K., Voss, E.U. [Indications and results of v.a.C therapy treatments in vascular surgery - state of the art in the treatment of chronic wounds]. [Article in German] *Zentralbl Chir* 2004; 129 Suppl 1, S74–S79.

**457** Pinocj, J., Albes, J.M., Wicke, C. et al. Treatment of periprosthetic soft tissue infection of the groin following vascular surgical procedures by means of a polyvinyl alcohol-vacuum sponge system. *Wound Repair Regen* 2003; 11: 2, 104–109.

**458** Tilgen, W., Mini-V.A.C.-therapy tots-Tuot, for secondary wound closure. *J Wound Healing*, 2000. Malignant tumours of the skin - The usefulness of the Mini-V.A.C.-therapy for secondary wound closure. *J Wound Healing* 2000; 13: 2.

**459** Rexer, M., Ditterich, D., Rupprecht, H. [V.a.C.-therapy in abdominal surgery - experiences, limits and indications]. [Article in German] *Zentralbl Chir* 2004; 129: Suppl 1, S27–S32.

**460** Ford-Dunn, S. Use of vacuum assisted closure therapy in the palliation of a malignant wound. *Palliat Med* 2006; 20: 4, 477–478.

**461** Riot, S., de Bonneceze, G., Garrido, I. et al. Is the use of negative pressure wound therapy for a malignant wound legitimate in a palliative context? The concept of NPWT ad vitam: A case series. *Palliat Med* 2015; 29: 5, 470–473.

**462** Matiaszek, J., Djedovic, G., Mattesich, M. et al. The combined use of NPWT and instillation using an octenidine based wound rinsing solution: a case study. *J Wound Care* 2014; 23: 11, 590–596.

**463** Stang, H.P. [Fast and effective VAC-therapy in abdominal wall infections and Fournier gangrene] [In Dutch]. *Eur Surg* 2003; 35: supplement 191.

**464** Zeininger, D. VAC-therapy of patients after streptococcus infections. *J Wound Healing* 2000; 13: 2, 48.

**465** Brinkert, D., Ali, M., Naud, M. et al. Negative pressure wound therapy with saline instillation: 131 patient case series. *Int Wound J* 2013; 10: s1 Suppl 1, 56–60.

**466** Willenegger, H. Local treatment of infections in traumatology. The irrigation-suction drainage system. Indication, principle of function and the technique of irrigation-suction drainage. *Aktuelle Probl Chir Orthop* 1979; 12: 68–70.

**467** Tao, Q., Ren, J., Ji, Z. et al. VAWCM-Instillation Improves Delayed Primary Fascial Closure of Open Septic Abdomen. *Gastroenterol Res Pract* 2014; 2014: 245182.

**468** Dondossola, D., Cavenago, M., Piconi, S. et al. Negative Pressure Wound Treatment of Infections Caused By Extensively Drug-Resistant Gram-Negative Bacteria After Liver Transplantation: Two Case Reports. *Transplant Proc* 2015; 47: 7, 2145–2149.

**469** Morodomi, Y., Takenoyama, M., Yamaguchi, M. et al. Application of continuous negative pressure irrigation and negative pressure fixation to treat a bronchopleural fistula with thoracic empyema. *J Am Coll Surg* 2014; 218: 5, e87–e90.

**470** Karaca, S., Kalangos, A. Vacuum-assisted closure (VAC)-Instill® with continuous irrigation for the treatment of *Mycoplasma hominis* mediastinitis. *Int Wound J* 2015; 12: 5, 595–597.

**471** Sziklavari, Z., Ried, M., Neu, R. et al. Mini-open vacuum-assisted closure therapy with instillation for debilitated and septic patients with pleural empyema. *Eur J Cardiothorac Surg* 2015; 48: 2, e9–e16.

**472** Sziklavari, Z., Ried, M., Hofmann, H.S. [Intrathoracic Vacuum-Assisted Closure in the Treatment of Pleural Empyema and Lung Abscess]. [Article in German] *Zentralbl Chir* 2015; 140: 3, 321–327.

**473** Meybodi, F., Sedaghat, N., French, J. et al. Implant salvage in breast reconstruction with severe peri-prosthetic infection. *ANZ J Surg* 2015 doi: 10.1111/ans.13379. [Epub ahead of print].

**474** Lehner, B., Fleischmann, W., Becker, R., Jukema, G.N. First experiences with negative pressure wound therapy and instillation in the treatment of infected orthopaedic implants: a clinical observational study. *Int Orthop* 2011; 35: 9, 1415–1420.

**475** Borrero Esteban, M.P., Begines Begines, R., Rodríguez Llamas, S., Díaz Campos, T. [Managing complications in severe traumatic injury with VAC therapy with instillation]. [Article in Spanish] *Rev Enferm* 2013; 36: 11, 42–47.

**476** Norris, R., Chapman, A.W., Krikler, S., Krkovic, M. A novel technique for the treatment of infected metalwork in orthopaedic patients using skin closure over irrigated negative pressure wound therapy dressings. *Ann R Coll Surg Engl* 2013; 95: 2, 118–124.

**477** Bollero, D., Degano, K., Gangemi, E.N. et al. Long-term follow-up of negative pressure wound therapy with instillation: a limb salvage procedure? *Int Wound J* 2016; 13: 5, 768–773.

**478** Sharr, P.J., Buckley, R.E. Current concepts review: open tibial fractures. *Acta Chir Orthop Traumatol Cech* 2014; 81: 2, 95–107.

**479** Temiz, G., Sirinoglu, H., Güvercin, E., Yesiloglu, N. et al. A useful option to obtain maximal foreign body removal and better prognosis in high pressure injection injuries: Negative pressure wound therapy with instillation. *J Plast Reconstr Aesthet Surg* 2016; 69: 4, 570–572.

**480** Crew, J.R., Varilla, R., Allandale Rocas Iii, T. et al. Treatment of acute necrotizing fasciitis using negative pressure wound therapy and adjunctive neutrophase irrigation under the foam. *Wounds* 2013; 25: 10, 272–277.

**481** Frankel, J.K., Rezaee, R.P., Harvey, D.J. et al. Use of negative pressure wound therapy with instillation in the management of cervical necrotizing fasciitis. *Head Neck* 2015; 37: 11, E157–E160.

- 482** Hu, S.X., Gold, D.M. Maximising vacuum drainage prior to wound closure. *Ann R Coll Surg Engl* 2015; 97: 1, 82.
- 483** Dalla Paola, L. Diabetic foot wounds: the value of negative pressure wound therapy with instillation. *Int Wound J* 2013; 10: s1 Suppl 1, 25–31.
- 484** Matiasek, J., Djedovic, G., Unger, L. et al. Outcomes for split-thickness skin transplantation in high-risk patients using octenidine. *J Wound Care* 2015; 24: 6 Suppl, S8, S10–S12.
- 485** Dale, A.P., Saeed, K. Novel negative pressure wound therapy with instillation and the management of diabetic foot infections. *Curr Opin Infect Dis* 2015; 2: 2, 151–157.
- 486** Hasan, M.Y., Teo, R., Nather, A. Negative-pressure wound therapy for management of diabetic foot wounds: a review of the mechanism of action, clinical applications, and recent developments. *Diabet Foot Ankle* 2015; 6: 27618.
- 487** Tian, G., Guo, Y., Zhang, L. Non-invasive treatment for severe complex pressure ulcers complicated by necrotizing fasciitis: a case report. *J Med Case Reports* 2015; 9: 1, 220.
- 488** Wen, H., Li, Z., Zhang, M. et al. [Effects of vacuum sealing drainage combined with irrigation of oxygen loaded fluid on wounds of patients with chronic venous leg ulcers]. [Article in Chinese] *Zhonghua Shao Shang Za Zhi* 2015; 31: 2, 86–92.
- 489** Yang, C.K., Alcantara, S., Goss, S., Lantis, J.C. 2nd. Cost analysis of negative-pressure wound therapy with instillation for wound bed preparation preceding split-thickness skin grafts for massive (>100cm<sup>2</sup>) chronic venous leg ulcers. *J Vasc Surg* 2015; 61: 4, 995–999.
- 490** Zhang, M., Li, Z., Wang, J. et al. [Effects of vacuum sealing drainage combined with irrigation of oxygen loaded fluid on chronic wounds in diabetic patients]. [Article in Chinese] *Zhonghua Shao Shang Za Zhi* 2014; 30: 2, 116–123.
- 491** Wolvos, T. Wound instillation the next step in negative pressure wound therapy. Lessons learned from initial experiences. *Ostomy Wound Manage* 2004; 50: 11, 56–66.
- 492** Morinaga, K., Kiyokawa, K., Rikimaru, H. et al. Results of intra-wound continuous negative pressure irrigation treatment for mediastinitis. *J Plast Surg Hand Surg* 2013; 47: 4, 297–302.
- 493** Derrick, K.L., Lessing, M.C. Genomic and proteomic evaluation of tissue quality of porcine wounds treated with negative pressure wound therapy in continuous, noncontinuous, and instillation modes. *Eplasty* 2014; 14: e43.
- 494** Allen, D., LaBarbera, L.A., Bondre, I.L. et al. Comparison of tissue damage, cleansing and cross-contamination potential during wound cleansing via two methods: lavage and negative pressure wound therapy with instillation. *Int Wound J* 2014; 11: 2, 198–209.
- 495** Kim, P.J., Attinger, C.E., Oliver, N. et al. Comparison of Outcomes for Normal Saline and an Antiseptic Solution for Negative-Pressure Wound Therapy with Instillation. *Plast Reconstr Surg* 2015; 136: 5, 657e–664e.
- 496** Timmers, M.S., Graafland, N., Bernards, A.T. et al. Negative pressure wound treatment with polyvinyl alcohol foam and polyhexanide antiseptic solution instillation in posttraumatic osteomyelitis. *Wound Repair Regen* 2009; 17: 2, 278–286.
- 497** Back, D.A., Scheuermann-Poley, C., Willy, C. Recommendations on negative pressure wound therapy with instillation and antimicrobial solutions - when, where and how to use: what does the evidence show? *Int Wound J* 2013; 10: s1 Suppl 1, 32–42.
- 498** Davis, K., Bills, J., Barker, J. et al. Simultaneous irrigation and negative pressure wound therapy enhances wound healing and reduces wound bioburden in a porcine model. *Wound Repair Regen* 2013; 21: 6, 869–875.
- 499** Nolfi, M.C., Layer, A., Meyer-Lindenberg, A. Negative pressure wound therapy with instillation for body wall reconstruction using an artificial mesh in a Dachshund. *Aust Vet J* 2015; 93: 10, 367–372.
- 500** Gabriel, A., Kahn, K.M. New advances in instillation therapy in wounds at risk for compromised healing. *Surg Technol Int* 2014; 24: 75–81.
- 501** Vowden, K., Pilcher, M. Early experience with instillation negative pressure wound therapy. *The EWMA 2015 conference* May 13, 2015; London: EWMA; 2015.
- 502** Jeong, H.S., Lee, B.H., Lee, H.K. et al. Negative pressure wound therapy of chronically infected wounds using 1% acetic Acid irrigation. *Arch Plast Surg* 2015; 42: 1, 59–67.
- 503** Wolvos, T. The use of negative pressure wound therapy with an automated, volumetric fluid administration: an advancement in wound care. *Wounds* 2013; 25: 3, 75–83.
- 504** Raad, W., Lantis, J.C. 2nd, Tyrie, L. et al. Vacuum-assisted closure instill as a method of sterilizing massive venous stasis wounds prior to split thickness skin graft placement. *Int Wound J* 2010; 7: 2, 81–85.
- 505** Hu, N., Wu, X.H., Liu, R. et al. Novel application of vacuum sealing drainage with continuous irrigation of potassium permanganate for managing infective wounds of gas gangrene. *J Huazhong Univ Sci Technolog Med Sci* 2015; 35: 4, 563–568.
- 506** Scimeca, C.L., Bharara, M., Fisher, T.K. et al. Novel use of doxycycline in continuous-instillation negative pressure wound therapy as wound chemotherapy. *Foot Ankle Spec* 2010; 3: 4, 190–193.
- 507** Wolvos, T. The evolution of negative pressure wound therapy: negative pressure wound therapy with instillation. *J Wound Care* 2015; 24: Sup4b Suppl, 15–20.
- 508** Scimeca, C.L., Bharara, M., Fisher, T.K. et al. Novel use of insulin in continuous-instillation negative pressure wound therapy as wound chemotherapy. *J Diabetes Sci Tech* 2010; 4: 4, 820–824.
- 509** Sun, Y., Fan, W., Yang, W. et al. [Effects of intermittent irrigation of insulin solution combined with continuous drainage of vacuum sealing drainage in chronic diabetic lower limb ulcers]. [Article in Chinese] *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi* 2015; 29: 7 812–817.
- 510** Rycerz, A.M., Allen, D., Lessing, M.C. Science supporting negative pressure wound therapy with instillation. *Int Wound J* 2013; 10: s1 Suppl 1, 20–24.
- 511** Kim, P.J., Attinger, C.E., Olawoye, O. et al. Negative pressure wound therapy with instillation: review of evidence and recommendations. *Wounds* 2015; 27: 12, S2–S19.
- 512** Fiorio, M., Marvaso, A., Viganò, F., Marchetti, F. Incidence of surgical site infections in general surgery in Italy. *Infection* 2006; 34: 6, 310–314.
- 513** Spindler, N., Lehmann, S., Steinau, H.U. et al. Complication management after interventions on thoracic organs. *Chirurg* 2015; 86: 3, 228–233.
- 514** Masden, D., Goldstein, J., Endara, M. et al. Negative pressure wound therapy for at-risk surgical closures in patients with multiple comorbidities: a prospective randomized controlled study. *Ann Surg* 2012; 255: 6, 1043–1047.
- 515** Howell, R.D., Hadley, S., Strauss, E., Pelham, F.R. Blister formation with

negative pressure dressings after total knee arthroplasty. *Curr Orthop Pract* 2011; 22: 2, 176–179.

**516** Semsarzadeh, N.N., Tadisina, K.K., Maddox, J. et al. Closed Incision Negative-Pressure Therapy Is Associated with Decreased Surgical-Site Infections. *Plast Reconstr Surg* 2015; 136: 3, 592–602.

**517** Wilkes, R.P., Kilpad, D.V., Zhao, Y. et al. Closed incision management with negative pressure wound therapy (CIM): biomechanics. *Surg Innov* 2012; 19: 1, 67–75.

**518** Meeker, J., Weinhold, P., Dahners, L. Negative pressure therapy on primarily closed wounds improves wound healing parameters at 3 days in a porcine model. *J Orthop Trauma* 2011; 25: 12, 756–761.

**519** Glaser, D.A., Farnsworth, C.L., Varley, E.S. et al. Negative pressure therapy for closed spine incisions: a pilot study. *Wounds* 2012; 24: 11, 308–316.

**520** Kilpadi, D.V., Cunningham, M.R. Evaluation of closed incision management with negative pressure wound therapy (CIM): Hematoma/seroma and involvement of the lymphatic system. *Wound Repair Regen* 2011; 19: 5, 588–596.

**521** Gurtner, G.C., Dauskardt, R.H., Wong, V.W. et al. Improving cutaneous scar formation by controlling the mechanical environment: large animal and phase I studies. *Ann Surg* 2011; 254: 2, 217–225.

**522** Timmenga, E., Andreassen, T., Houthoff, H., Klopfer, P. The effect of mechanical stress on healing skin wounds: an experimental study in rabbits using tissue expansion. *Br J Plast Surg* 1991; 44: 7, 514–519.

**523** Baaijens, F., Bouten, C., Driessen, N. Modeling collagen remodeling. *J Biomech* 2010; 43: 1, 166–175.

**524** Driessen, N., Peters, G., Huyghe, J. et al. Remodelling of continuously distributed collagen fibres in soft connective tissues. *J Biomech* 2003; 36: 8, 1151–1158.

**525** Hinz, B., Mastrangelo, D., Iselin, C.E. et al. Mechanical tension controls granulation tissue contractile activity and myofibroblast differentiation. *Am J Pathol* 2001; 159: 3, 1009–1020.

**526** van der Veer, W.M., Bloemen, M.C., Ulrich, M.M. et al. Potential cellular and molecular causes of hypertrophic scar formation. *Burns* 2009; 35: 1, 15–29.

**527** Aarabi, S., Bhatt, K.A., Shi, Y. et al. Mechanical load initiates hypertrophic scar formation through decreased cellular apoptosis. *FASEB J* 2007; 21: 12, 3250–3261.

**528** Stannard, J.P., Volgas, D.A., McGwin, G. 3rd. et al. Incisional negative pressure wound therapy after high-risk lower extremity fractures. *J Orthop Trauma* 2012; 26: 1, 37–42.

**529** Pachowsky, M., Gusinde, J., Klein, A. et al. Negative pressure wound therapy to prevent seromas and treat surgical incisions after total hip arthroplasty. *Int Orthop* 2012; 36: 4, 719–722.

**530** Nordmeyer, M., Pauser, J., Biber, R. et al. Negative pressure wound therapy for seroma prevention and surgical incision treatment in spinal fracture care. *Int Wound J* 2016; 13: 6, 1176–1179.

**531** Pauser, J., Nordmeyer, M., Biber, R. et al. Incisional negative pressure wound therapy after hemiarthroplasty for femoral neck fractures - reduction of wound complications. *Int Wound J* 2016; 13: 5, 663–667.

**532** Cutting, K.F., Harding, K.G. Criteria for identifying wound infection. *J Wound Care* 1994; 3: 4, 198–201.

**533** Farley Verner, E., Musher, D.M. Spinal epidural abscess. *Med Clin*

*North Am* 1985; 69: 2, 375–384.

**534** Ingargiola, M.J., Daniali, L.N., Lee, E.S. Does the application of incisional negative pressure therapy to high-risk wounds prevent surgical site complications? A systematic review. *Eplasty* 2013; 13: e49.

**535** Reddix, R.N. Jr., Tyler, H.K., Kulp, B., Webb, L.X. Incisional vacuum-assisted wound closure in morbidly obese patients undergoing acetabular fracture surgery. *Am J Orthop (Belle Mead NJ)* 2009; 38: 9, 446–449.

**536** Blackham, A.U., Farrah, J.P., McCoy, T.P. et al. Prevention of surgical site infections in high-risk patients with laparotomy incisions using negative-pressure therapy. *Am J Surg* 2013; 205: 6, 647–654.

**537** Bonds, A.M., Novick, T.K., Dietert, J.B. et al. Incisional negative pressure wound therapy significantly reduces surgical site infection in open colorectal surgery. *Dis Colon Rectum* 2013; 56: 12, 1403–1408.

**538** Chadi, S.A., Kidane, B., Britto, K. et al. Incisional negative pressure wound therapy decreases the frequency of postoperative perineal surgical site infections: a cohort study. *Dis Colon Rectum* 2014; 57: 8, 999–1006.

**539** Pellino, G., Sciaudone, G., Candilio, G. et al. Preventive NPWT over closed incisions in general surgery: Does age matter? *Int J Surg* 2014; 12 Suppl 2, S64–S68.

**540** Selvaggi, F., Pellino, G., Sciaudone, G. et al. New advances in negative pressure wound therapy (NPWT) for surgical wounds of patients affected with Crohns disease. *Surg Technol Int* 2014; 24: 83–89.

**541** Vargo, D. Negative pressure wound therapy in the prevention of wound infection in high risk abdominal wound closures. *Am J Surg* 2012; 204: 6, 1021–1024.

**542** Mark, K.S., Alger, L., Terplan, M. Incisional negative pressure therapy to prevent wound complications following cesarean section in morbidly obese women: a pilot study. *Surg Innov* 2014; 21: 4, 345–349.

**543** Hickson, E., Harris, J., Brett, D.A. Journey to zero: reduction of post-operative cesarean surgical site infections over a five-year period. *Surg Infect (Larchmt)* 2015; 16: 2, 174–177.

**544** Bullough, L., Wilkinson, D., Burns, S., Wan, L. Changing wound care protocols to reduce postoperative caesarean section infection and readmission. *Wounds UK* 2014; 10: 1, 72–76.

**545** Chaboyer, W., Anderson, V., Webster, J. et al. Negative pressure wound therapy on surgical site infections in women undergoing elective caesarean sections: a Pilot RCT. *Health Care (Don Mills)* 2014; 2: 4, 417–428.

**546** Matsumoto, T., Parekh, S.G. Use of Negative Pressure Wound Therapy on Closed Surgical Incision After Total Ankle Arthroplasty. *Foot Ankle Int* 2015; 36: 7, 787–794.

**547** Condé-Green, A., Chung, T.L., Holton, L.H. 3rd. et al. Incisional negative-pressure wound therapy versus conventional dressings following abdominal wall reconstruction: a comparative study. *Ann Plast Surg* 2013; 71: 4, 394–397.

**548** Grauhan, O., Navasardyan, A., Tutkun, B. et al. Effect of surgical incision management on wound infections in a poststernotomy patient population. *Int Wound J* 2014; 11: s1 Suppl 1, 6–9.

**549** Pauli, E.M., Krpata, D.M., Novitsky, Y.W., Rosen, M.J. Negative pressure therapy for high-risk abdominal wall reconstruction incisions. *Surg Infect (Larchmt)* 2013; 14: 3, 270–274.

**550** Karlakki, S., Brem, M., Giannini, S. et al. Negative pressure wound therapy for management of the surgical incision in orthopaedic surgery: A review of evidence and mechanisms for an emerging indication. *Bone Joint*

Res 2013; 2: 12, 276–284.

**551** Hwang, K.T., Kim, S.W., Sung, I.H. et al. Is delayed reconstruction using the latissimus dorsi free flap a worthy option in the management of open IIIB tibial fractures? *Microsurgery* 2016; 36: 6, 453–459.

**552** Stannard, J.P., Singanamala, N., Volgas, D.A. Fix and flap in the era of vacuum suction devices: What do we know in terms of evidence based medicine? *Injury* 2010; 41: 8, 780–786.

**553** Mehta, S., Williams, W. Fix and flap: the radical orthopaedic and plastic treatment of severe open fractures of the tibia. *J Bone Joint Surg Br* 2001; 83: 5, 773–774.

**554** Hou, Z., Irgit, K., Strohecker, K.A. et al. Delayed flap reconstruction with vacuum-assisted closure management of the open IIIB tibial fracture. *J Trauma* 2011; 71: 6, 1705–1708.

**555** Bhattacharyya, T., Mehta, P., Smith, M., Pomahac, B. Routine use of wound vacuum-assisted closure does not allow coverage delay for open tibia fractures. *Plast Reconstr Surg* 2008; 121: 4, 1263–1266.

**556** Steiert, A.E., Gohritz, A., Schreiber, T.C. et al. Delayed flap coverage of open extremity fractures after previous vacuum-assisted closure (VAC®) therapy – worse or worth? *J Plast Reconstr Aesthet Surg* 2009; 62: 5, 675–683.

**557** McSweeney, A.J., Creer, T.L. Health-related quality-of-life assessment in medical care. *Dis Mon* 1995; 41: 1, 6–71.

**558** Patrick, D.L., Deyo, R.A. Generic and disease-specific measures in assessing health status and quality of life. *Med Care* 1989; 27: 3 Supplement, S217–S232.

**559** Ousey, K., Cook, L., Milne, J. Negative pressure wound therapy—does it affect quality of life? *Wounds UK* 2012; 8: 4, 18–28.

**560** Ousey, K.J., Milne, J., Cook, L. et al. A pilot study exploring quality of life experienced by patients undergoing negative-pressure wound therapy as part of their wound care treatment compared to patients receiving standard wound care. *Int Wound J* 2014; 11: 4, 357–365.

**561** Mendonca, D.A., Drew, P.J., Harding, K.G., Price, R.E. A pilot study on the effect of topical negative pressure on quality of life. *J Wound Care* 2007; 16: 2, 49–53.

**562** Wallin, A.M., Boström, L., Ulfvarson, J., Ottosson, C. Negative pressure wound therapy - a descriptive study. *Ostomy Wound Manage* 2011; 57: 6, 22–29.

**563** Fagerdahl, A.M., Bostrom, L., Ulfvarson, J., Ottosson, C. Risk Factors for Unsuccessful Treatment and Complications With Negative Pressure Wound Therapy. *Wounds* 2012; 24: 6, 168–177.

**564** Lindholm, C., Bjellerup, M., Christensen, O.B., Zederfeldt, B. Quality of life in chronic leg ulcer patients. An assessment according to the Nottingham Health Profile. *Acta Derm Venereol* 1993; 73: 6, 440–443.

**565** Price, P.E., Fagervik-Morton, H., Mudge, E.J. et al. Dressing-related pain in patients with chronic wounds: an international patient perspective. *Int Wound J* 2008; 5: 2, 159–171.

**566** Fagerdahl, A.M., Boström, L., Ottosson, C., Ulfvarson, J. Patients experience of advanced wound treatment—a qualitative study. *Wounds* 2013; 25: 8, 205–211.

**567** Christensen, T.J., Thorum, T., Kubiak, E.N. Lidocaine analgesia for removal of wound vacuum-assisted closure dressings: a randomized double-blinded placebo-controlled trial. *J Orthop Trauma* 2013; 27: 2, 107–112.

**568** Findikcioglu, K., Sezgin, B., Kaya, B. et al. The effect of regional block over pain levels during vacuum-assisted wound closure. *Int Wound J* 2014; 11: 1, 69–73.

**569** Bolas, N., Holloway, S. Negative pressure wound therapy: a study on patient perspectives. *Br J Community Nurs* 2012; 17: Sup3 Suppl, S30–S35.

**570** Fagerdahl, A.M. The patient's conceptions of wound treatment with negative pressure wound therapy. *Healthcare* 2014; 2: 3, 272–281.

**571** Ousey, K.J., Milne, J. Exploring portable negative pressure wound therapy devices in the community. *Br J Community Nurs* 2014; Suppl S14–S20.

**572** Andrews, A., Upton, D. Negative pressure wound therapy: improving the patient experience part 3 of 3. *J Wound Care*. 2013; 22: 12, 671–680.

**573** Keskin, M., Karabekmez, F.E., Yilmaz, E. et al. Vacuum-assisted closure of wounds and anxiety. *Scand J Plast Reconstr Surg Hand Surg* 2008; 42: 4, 202–205.

**574** Abbotts, J. Patients views on topical negative pressure: effective but smelly. *Br J Nurs* 2010; 19: Sup10, S37–S41.

**575** Ottosen, B., Pedersen, B.D. Patients' experiences of NPWT in an outpatient setting in Denmark. *J Wound Care* 2013; 22: 4, 197–206.

**576** Food and Drug Administration. Medical devices; general and plastic surgery devices; classification of non-powered suction apparatus device intended for negative pressure wound therapy. Final rule. *Fed Regist* 2010; 75: 221, 70112–70114.

**577** Martindell, D. The safe use of negative-pressure wound therapy. *Am J Nurs* 2012; 112: 6, 59–63.

**578** Sullivan, N., Snyder, D.L., Tipton, K. et al. Technology Assessment report: negative pressure wound therapy devices. 2009. In: *Negative pressure wound therapy devices*. AHRQ Technology Assessments. <https://tinyurl.com/hm3xlb> (accessed 1 March 2017).

**579** Ricci, E., Messina, R., Bonanante, M.P. Reimbursement in Italy. *Journal of Wound Technology* 2008; 1: 46–48.

**580** Bartkowski, R. [Length of hospital stay due to DRG reimbursement]. [Article in German] *Ther Umsch* 2012; 69: 1, 15–21.

**581** Bliss, D.Z., Westra, B.L., Savik, K., Hou, Y. Effectiveness of wound, ostomy and continence-certified nurses on individual patient outcomes in home health care. *Home Healthc Nurse* 2014; 32: 1, 31–38.

**582** Schaum, K.D. A new Medicare Part B wound care policy. *Adv Skin Wound Care* 2001; 14: 5, 238–240.

**583** Hurd, T., Trueman, P., Rossington, A. Use of a portable, single-use negative pressure wound therapy device in home care patients with low to moderately exuding wounds: a case series. *Ostomy Wound Manage* 2014; 60: 3, 30–36.

**584** Williams, K. Developing a strategic framework to implement a managed service for NPWT. In: Bassetto, F., Bruhin, A., Trueman, P. et al. (eds). *Template for management: developing a negative pressure wound therapy service*. *Wounds International*, 2010.

**585** Woo, K.Y., Sibbald, R.G. Vacuum-assisted closure home care training: a process to link education to improved patient outcomes. *Int Wound J* 2008; 5: S2 Suppl 2, 1–9.

**586** Moffatt, C.J., Mapplebeck, L., Murray, S., Morgan, P.A. The experience of patients with complex wounds and the use of NPWT in a home-care setting. *J Wound Care* 2011; 20: 11, 512–527.

- 587** Teot, L. Editorial. *Journal of Wound Technology* 2009; 5.
- 588** US Food and Drug Administration (FDA). (2009) FDA preliminary public health notification: serious complications associated with negative pressure wound therapy systems. <https://tinyurl.com/zuvvzk3> (accessed 1 March 2017).
- 589** Nursing and Midwifery Council (NMC). (2009) Record keeping: guidance for nurses and midwives. <https://tinyurl.com/jfkxaw6> (accessed 1 March 2017).
- 590** Vowden, K., Vowden, P. Documentation in pressure ulcer prevention and management. *Wounds UK* 2015; 11: 3, 6–9.
- 591** White, R., Bennett, D., Bree-Aslan, C., Downie, F. Debate: Pressure ulcers, negligence and litigation. *Wounds UK* 2015; 11: 1, 8–14.
- 592** Lawson, S. Getting the record straight: the need for accurate documentation. *J Wound Care* 2004; 13: 10, 427.
- 593** Culley, F. The tissue viability nurse and effective documentation. *Br J Nurs* 2001; 10: Sup3 Suppl, S30–S39.
- 594** Vowden, K. Cavity wounds. *J Wound Care* submitted 2015.
- 595** Leijnen, M., Steenvoorde, P.A retained sponge is a complication of vacuum-assisted closure therapy. *Int J Low Extrem Wounds* 2008; 7: 1, 51.
- 596** Bayne, D., Martin, N.A simple method to prevent vacuum-assisted closure sponge retention in cavity wounds. *Wounds* 2014; 26: 7, E53–E54.
- 597** Albert, N.M., Rock, R., Sammon, M.A. et al. Do patient and nurse outcome differences exist between 2 negative pressure wound therapy systems? *J Wound Ostomy Continence Nurs* 2012; 39: 3, 259–266.
- 598** Le Franc, B., Sellal, O., Grimandi, G., Duteille, F. [Cost-effectiveness analysis of vacuum-assisted closure in the surgical wound bed preparation of soft tissue injuries]. [Article in French] *Ann Chir Plast Esthet* 2010; 55: 3, 195–203.
- 599** Trujillo-Martín, M., García-Pérez, L., Serrano-Aguilar, P. [Effectiveness, safety and cost-effectiveness of the negative pressure wound therapy on the treatment of chronic wounds: a systematic review]. [Article in Spanish] *Med Clin (Barc)* 2011; 137: 7, 321–328.
- 600** Boulton, A.J., Vileikyte, L., Ragnarson-Tennvall, G., Apelqvist, J. The global burden of diabetic foot disease. *Lancet* 2005; 366: 9498, 1719–1724.
- 601** Driver, V.R., Fabbi, M., Lavery, L.A., Gibbons, G. The costs of diabetic foot: The economic case for the limb salvage team. *J Vasc Surg* 2010; 52: 3 Suppl, 17S–22S.
- 602** Moore, Z., Butcher, G., Corbett, L. et al. Managing wounds as a team—exploring the concept of a team approach to wound care. *J Wound Care* 2014; 23: 5 suppl, 1–38.
- 603** Prompers, L., Huijberts, M., Schaper, N. et al. Resource utilisation and costs associated with the treatment of diabetic foot ulcers. Prospective data from the Eurodiale Study. *Diabetologia* 2008; 51: 10, 1826–1834.
- 604** Apelqvist, J., Ragnarson-Tennvall, G., Larsson, J., Persson, U. Diabetic foot ulcers in a multidisciplinary setting An economic analysis of primary healing and healing with amputation. *J Intern Med* 1994; 235: 5, 463–471.
- 605** Eneroth, M., Larsson, J., Apelqvist, J. et al. The challenge of multicenter studies in diabetic patients with foot infections. *Foot* 2004; 14: 4, 198–203.
- 606** Girod, I., Valensi, P., Laforêt, C. et al. An economic evaluation of the cost of diabetic foot ulcers: results of a retrospective study on 239 patients. *Diabetes Metab* 2003; 29: 3, 269–277.
- 607** Gordois, A., Scuffham, P., Shearer, A. et al. The health care costs of diabetic peripheral neuropathy in the US. *Diabetes Care* 2003; 26: 6, 1790–1795.
- 608** Houtum, W.H., Lavery, L.A., Harkless, L.B. The costs of diabetes-related lower extremity amputations in the Netherlands. *Diabet Med* 1995; 12: 9, 777–781.
- 609** Krishnan, S., Nash, F., Baker, N. et al. Reduction in Diabetic Amputations Over 11 Years in a Defined U.K. Population: Benefits of multidisciplinary team work and continuous prospective audit. *Diabetes Care* 2008; 31: 1, 99–101.
- 610** Ortegón, M.M., Redekop, W.K., Niessen, L.W. Cost-effectiveness of prevention and treatment of the diabetic foot: a Markov analysis. *Diabetes Care* 2004; 27: 4, 901–907.
- 611** Rauner, M.S., Heidenberger, K., Pesendorfer, E.M. (2004) Using a Markov model to evaluate the cost-effectiveness of diabetic foot prevention strategies in Austria. Proceedings of the Western Multiconference, International Conference on Health Sciences Simulation. <https://tinyurl.com/ztryz4m> (accessed 1 March 2017).
- 612** Ragnarson Tennvall, G., Apelqvist, J. Prevention of diabetes-related foot ulcers and amputations: a cost-utility analysis based on Markov model simulations. *Diabetologia* 2001; 44: 11: 2077–2087.
- 613** Van Acker, K., Oleen-Burkey, M., De Decker, L. et al. Cost and resource utilization for prevention and treatment of foot lesions in a diabetic foot clinic in Belgium. *Diabetes Res Clin Pract* 2000; 50: 2, 87–95.
- 614** Öien, R.F., Ragnarson Tennvall, G.J. Accurate diagnosis and effective treatment of leg ulcers reduce prevalence, care time and costs. *J Wound Care* 2006; 15: 6, 259–262.
- 615** Apelqvist, J. Health Economics and Hard to Heal Ulcers. *Journal of Wound Technology* 2010 9: III, 50–55.
- 616** Apelqvist, J., Aron, S., Edwards, H., Carter, M. International consensus. Making the case for cost-effective wound management. *Wounds Int* 2013.
- 617** Olin, J.W., Beusterien, K.M., Childs, M.B. et al. Medical costs of treating venous stasis ulcers: evidence from a retrospective cohort study. *Vasc Med* 1999; 4: 1, 1–7.
- 618** Posnett, J., Franks, P. The costs of skin breakdown and ulceration in the UK. *Skin Breakdown—the silent epidemic*. The Smith and Nephew Foundation. 2007.
- 619** Ragnarson-Tennvall, G., Apelqvist, J. Cost-effective management of diabetic foot ulcers: a review. *Pharmacoeconomics* 1997; 12: 1, 42–53.
- 620** Buxton, M.J., Drummond, M.F., Van Hout, B.A. et al. Modelling in economic evaluation: an unavoidable fact of life. *Health Econ* 1997; 6: 3, 217–227.
- 621** Drummond, M., Pang, F. Transferability of economic evaluation results. In: *Economic evaluation in health care: merging theory with practice*. Oxford University Press, 2001.
- 620** Vacuum-assisted closure for chronic wound healing. *Tecnologica MAP Suppl* 2000: 19–20.
- 622** Dougherty, E.J. An evidence-based model comparing the cost-effectiveness of platelet-rich plasma gel to alternative therapies for patients with nonhealing diabetic foot ulcers. *Adv Skin Wound Care* 2008; 21: 12, 568–575.
- 623** Echebiri, N.C., McDoom, M.M., Aalto, M.M. et al. Prophylactic use of negative pressure wound therapy after cesarean delivery. *Obstet Gynecol*

2015; 125: 2, 299–307.

- 624** Flack, S., Apelqvist, J., Keith, M. et al. An economic evaluation of VAC therapy compared with wound dressings in the treatment of diabetic foot ulcers. *J Wound Care* 2008; 17: 2, 71–78.
- 625** Gabriel, A., Kahn, K., Karmy-Jones, R. Use of negative pressure wound therapy with automated, volumetric instillation for the treatment of extremity and trunk wounds: clinical outcomes and potential cost-effectiveness. *Eplasty* 2014; 14: e41.
- 626** Lavery, L.A., Boulton, A.J., Niezgod, J.A., Sheehan, P.A. comparison of diabetic foot ulcer outcomes using negative pressure wound therapy versus historical standard of care. *Int Wound J* 2007; 4: 2, 103–113.
- 627** Lewis, L.S., Convery, P.A., Bolac, C.S. et al. Cost of care using prophylactic negative pressure wound vacuum on closed laparotomy incisions. *Gynecol Oncol* 2014; 132: 3, 684–689.
- 628** Tuffaha, H.W., Gillespie, B.M., Chaboyer, W. et al. Cost-utility analysis of negative pressure wound therapy in high-risk cesarean section wounds. *J Surg Res* 2015; 195: 2, 612–622.
- 629** Whitehead, S.J., Forest-Bendien, V.L., Richard, J.L. et al. Economic evaluation of Vacuum Assisted Closure® Therapy for the treatment of diabetic foot ulcers in France. *Int Wound J* 2011; 8: 1, 22–32.
- 630** Health Quality Ontario. Negative pressure wound therapy: an evidence update. *Ont Health Technol Assess Ser* 2010; 10: 22, 1–28.
- 631** Soares, M.O., Bojke, L., Dumville, J. et al. Methods to elicit experts beliefs over uncertain quantities: application to a cost effectiveness transition model of negative pressure wound therapy for severe pressure ulceration. *Stat Med* 2011; 30: 19, 2363–2380.
- 632** Inhoff, O., Faulhaber, J., Rothhaar, B. et al. Analysis of treatment costs for complex scalp wounds. *J Dtsch Dermatol Ges* 2010; 8: 11, 890–896.
- 633** Rhee, S.M., Valle, M.F., Wilson, L.M. et al. Negative pressure wound therapy technologies for chronic wound care in the home setting: A systematic review. *Wound Repair Regen* 2015; 23: 4, 506–517.
- 634** Searle, R., Milne, J. Tools to compare the cost of NPWT with advanced wound care: an aid to clinical decision-making. *Wounds UK* 2010; 6: 1, 106–109.
- 635** Ali, Z., Anjum, A., Khurshid, L. et al. Evaluation of low-cost custom made VAC therapy compared with conventional wound dressings in the treatment of non-healing lower limb ulcers in lower socio-economic group patients of Kashmir valley. *J Orthop Surg* 2015; 10: 1, 183.
- 636** Apelqvist, J., Armstrong, D.G., Lavery, L.A., Boulton, A.J. Resource utilization and economic costs of care based on a randomized trial of vacuum-assisted closure therapy in the treatment of diabetic foot wounds. *Am J Surg* 2008; 195: 6, 782–788.
- 637** Aydin, U., Gorur, A., Findik, O. et al. Therapeutic efficacy of vacuum-assisted-closure therapy in the treatment of lymphatic complications following peripheral vascular interventions and surgeries. *Vascular* 2015; 23: 1, 41–46.
- 638** Baharestani, M.M., Houliston-Otto, D.B., Barnes, S. Early versus late initiation of negative pressure wound therapy: examining the impact on home care length of stay. *Ostomy Wound Manage* 2008; 54: 11, 48–53.
- 639** Braakenburg, A., Obdeijn, M.C., Feitz, R. et al. The clinical efficacy and cost effectiveness of the vacuum-assisted closure technique in the management of acute and chronic wounds: a randomized controlled trial. *Plast Reconstr Surg* 2006; 118: 2, 390–397.
- 640** de Leon, J.M., Barnes, S., Nagel, M. et al. Cost-effectiveness of negative pressure wound therapy for postsurgical patients in long-term acute care. *Adv Skin Wound Care* 2009; 22: 3, 122–127.
- 641** Dorafshar, A.H., Franczyk, M., Gottlieb, L.J. et al. A prospective randomized trial comparing subatmospheric wound therapy with a sealed gauze dressing and the standard vacuum-assisted closure device. *Ann Plast Surg* 2012; 69: 1, 79–84.
- 642** Driver, V.R., Blume, P.A. Evaluation of wound care and health-care use costs in patients with diabetic foot ulcers treated with negative pressure wound therapy versus advanced moist wound therapy. *J Am Podiatr Med Assoc* 2014; 104: 2, 147–153.
- 643** Ghatak, P.D., Schlanger, R., Ganesh, K. et al. A wireless electroceutical dressing lowers cost of negative pressure wound therapy. *Adv Wound Care* 2015; 4: 5, 302–311.
- 644** Hermans, M.H., Kwon, Lee, S., Ragan, M.R., Laudi, P. Results of a retrospective comparative study: material cost for managing a series of large wounds in subjects with serious morbidity with a hydrokinetic fiber dressing or negative pressure wound therapy. *Wounds* 2015; 27: 3, 73–82.
- 645** Hiskett, G. Clinical and economic consequences of discharge from hospital with on-going TNP therapy: a pilot study. *J Tissue Viability* 2010; 19: 1, 16–21.
- 646** Kaplan, M., Daly, D., Stelmowski, S. Early intervention of negative pressure wound therapy using vacuum-assisted closure in trauma patients: impact on hospital length of stay and cost. *Adv Skin Wound Care* 2009; 22: 3, 128–132.
- 647** Karr, J.C., de Mola, F.L., Pham, T., Tooke, L. Wound healing and cost-saving benefits of combining negative-pressure wound therapy with silver. *Adv Skin Wound Care* 2013; 26: 12, 562–565.
- 648** Law, A., Cyhaniuk, A., Krebs, B. Comparison of health care costs and hospital readmission rates associated with negative pressure wound therapies. *Wounds* 2015; 27: 3, 63–72.
- 649** Ozturk, E., Ozguc, H., Yilmazlar, T. The use of vacuum assisted closure therapy in the management of Fourniers gangrene. *Am J Surg* 2009; 197: 5, 660–665.
- 650** Rahmanian-Schwarz, A., Willkomm, L.M., Gonser, P. et al. A novel option in negative pressure wound therapy (NPWT) for chronic and acute wound care. *Burns* 2012; 38: 4, 573–577.
- 651** Sakellariou, V.I., Mavrogenis, A.F., Papagelopoulos, P.J. Negative-pressure wound therapy for musculoskeletal tumor surgery. *Adv Skin Wound Care* 2011; 24: 1, 25–30.
- 652** Vaidhya, N., Panchal, A., Anchalia, M.M. A New Cost-effective method of npwt in diabetic foot wound. *Indian J Surg* 2015; 77: Suppl 2, 525–529.
- 653** Warner, M., Henderson, C., Kadmas, W., Mitchell, D.T. Comparison of vacuum-assisted closure to the antibiotic bead pouch for the treatment of blast injury of the extremity. *Orthopaedics* 2010; 33: 2, 77–82.
- 654** Yao, M., Fabbri, M., Hayashi, H. et al. A retrospective cohort study evaluating efficacy in high-risk patients with chronic lower extremity ulcers treated with negative pressure wound therapy. *Int Wound J* 2014; 11: 5, 483–488.
- 655** Zhou, Z.Y., Liu, Y.K., Chen, H.L., Liu, F. Prevention of surgical site infection after ankle surgery using vacuum-assisted closure therapy in high-risk patients with diabetes. *J Foot Ankle Surg* 2016; 55: 1, 129–131.
- 656** Anthony, H. Efficiency and cost effectiveness of negative pressure wound therapy. *Nurs Stand* 2015; 30: 8, 64–70.



- 657** Chaput, B., Garrido, I., Eburdery, H. et al. Low-cost negative-pressure wound therapy using wall vacuum: a 15 dollars by day alternative. *Plast Reconstr Surg Glob Open* 2015; 3: 6, e418.
- 658** Rozen, W.M., Shahbaz, S., Morsi, A. An improved alternative to vacuum-assisted closure (VAC) as a negative pressure dressing in lower limb split skin grafting: A clinical trial. *J Plast Reconstr Aesthet Surg* 2008; 61: 3, 334–337.
- 659** Shalom, A., Eran, H., Westreich, M., Friedman T. Our experience with a homemade vacuum-assisted closure system. *Isr Med Assoc J* 2008; 10: 8–9, 613–616.
- 660** Verhaalen, A., Watkins, B., Brasel K. Techniques and cost effectiveness of enteroatmospheric fistula isolation. *Wounds* 2010; 22: 8, 212–217.
- 661** Webster, J., Scuffham, P., Stankiewicz, M., Chaboyer, W.P. Negative pressure wound therapy for skin grafts and surgical wounds healing by primary intention. *Cochrane Database Syst Rev* 2014; 10: CD009261.
- 662** Augustin, M., Zschocke, I. Patient evaluation of the benefit of outpatient and inpatient vacuum therapy. Multicenter study with patient-relevant end points. *MMW Fortschr Med* 2006; 148: 25–32.
- 663** Braakenburg, A., Obdeijn, M.C., Feitz, R. et al. The clinical efficacy and cost effectiveness of the vacuum-assisted closure technique in the management of acute and chronic wounds: a randomized controlled trial. *Plast Reconstr Surg* 2006; 118: 2, 390–397.
- 664** Vuerstaek, J.D., Vainas, T., Wuite, J. et al. State-of-the-art treatment of chronic leg ulcers: A randomized controlled trial comparing vacuum-assisted closure (V.A.C.) with modern wound dressings. *J Vasc Surg* 2006; 44: 5, 1029–1037.
- 665** Khanbhai, M., Fosah, R., Oddy, M.J., Richards, T. Disposable NPWT device to facilitate early patient discharge following complex DFU. *J Wound Care*. 2012; 21: 4, 180–182.
- 666** Sinha, S., Mudge, E. The national health-care agenda in relation to negative pressure wound therapy. *Br J Community Nurs* 2013; Suppl: S6–S13.
- 667** Canadian Agency for Drugs and Technologies in Health. (2014) Negative pressure wound therapy for managing diabetic foot ulcers: a review of the clinical effectiveness, cost-effectiveness, and guidelines. Rapid response report: summary with critical appraisal. <https://tinyurl.com/hq7ato6> (accessed 1 March 2017).
- 668** Ousey, K., Milne, J. Focus on negative pressure: exploring the barriers to adoption. *Br J Community Nurs* 2010; 15: 3, 121–124.
- 669** Othman, D. Negative pressure wound therapy literature review of efficacy, cost effectiveness, and impact on patients' quality of life in chronic wound management and its implementation in the United Kingdom. *Plastic Surg Int* 2012; 2012: 374398.
- 670** Wu, S.C., Armstrong, D.G. Clinical outcome of diabetic foot ulcers treated with negative pressure wound therapy and the transition from acute care to home care. *Int Wound J* 2008; 5: s2 Suppl 2, 10–16.
- 671** Hampton J. Providing cost-effective treatment of hard-to-heal wounds in the community through use of NPWT. *Br J Community Nurs* 2015; Suppl Community Wound Care: S14–S20.
- 672** Khanbhai, M., Fosah, R., Oddy, M.J., Richards, T. Disposable NPWT device to facilitate early patient discharge following complex DFU. *J Wound Care* 2012; 21: 4, 180–182.
- 673** Kim, P.J., Attinger, C.E., Steinberg, J.S. et al. Negative-pressure wound therapy with instillation: international consensus guidelines. *Plast Reconstr Surg* 2013; 132: 6, 1569–1579.
- 674** Gabriel, A., Thimmappa, B., Rubano, C., Storm-Dickerson T. Evaluation of an ultra-lightweight, single-patient-use negative pressure wound therapy system over dermal regeneration template and skin grafts. *Int Wound J* 2013; 10: 4, 418–424.
- 675** Hudson, D.A., Adams, K.G., Van Huyssteen, A. et al. Simplified negative pressure wound therapy: clinical evaluation of an ultraportable, no-canister system. *Int Wound J* 2015; 12: 2, 195–201.
- 676** Holt, R., Murphy, J. PICO™ incision closure in oncoplastic breast surgery: a case series. *Br J Hosp Med* 2015; 76: 4, 217–223.
- 677** Pellino, G., Sciaudone, G., Selvaggi, F., Canonico, S. Prophylactic negative pressure wound therapy in colorectal surgery. Effects on surgical site events: current status and call to action. *Updates in Surgery* 2015; 67: 3, 235–245.
- 678** Fraccalvieri, M., Zingarelli, E., Ruka, E. et al. Negative pressure wound therapy using gauze and foam: histological, immunohistochemical and ultrasonography morphological analysis of the granulation tissue and scar tissue. Preliminary report of a clinical study. *Int Wound J* 2011; 8: 4, 355–364.
- 679** Salvo, P., Dini, V., Di Francesco, F., Romanelli, M. The role of biomedical sensors in wound healing. *Wound Medicine* 2015; 8: 15–18.
- 680** SWAN iCare. SWAN iCare project objectives. <https://tinyurl.com/jqts2js> (accessed 1 March 2017).
- 681** Pantelopoulos, A., Bourbakis, N.G. A survey on wearable sensor-based systems for health monitoring and prognosis. *IEEE Trans Syst Man Cybern C* 2010; 40: 1, 1–12.
- 682** Hall, B.H., Khan, B. (2003) Adoption of new technology. National Bureau of Economic Research. <https://tinyurl.com/g54sqgy> (accessed 1 March 2017).
- 683** Ousey, K.J., Milne, J. Exploring portable negative pressure wound therapy devices in the community. *Br J Community Nurs* 2014; Suppl: S14–20.
- 684** Davis, M.M., Freeman, M., Kaye, J. et al. A systematic review of clinician and staff views on the acceptability of incorporating remote monitoring technology into primary care. *Telemed J E Health* 2014; 20: 5, 428–438.

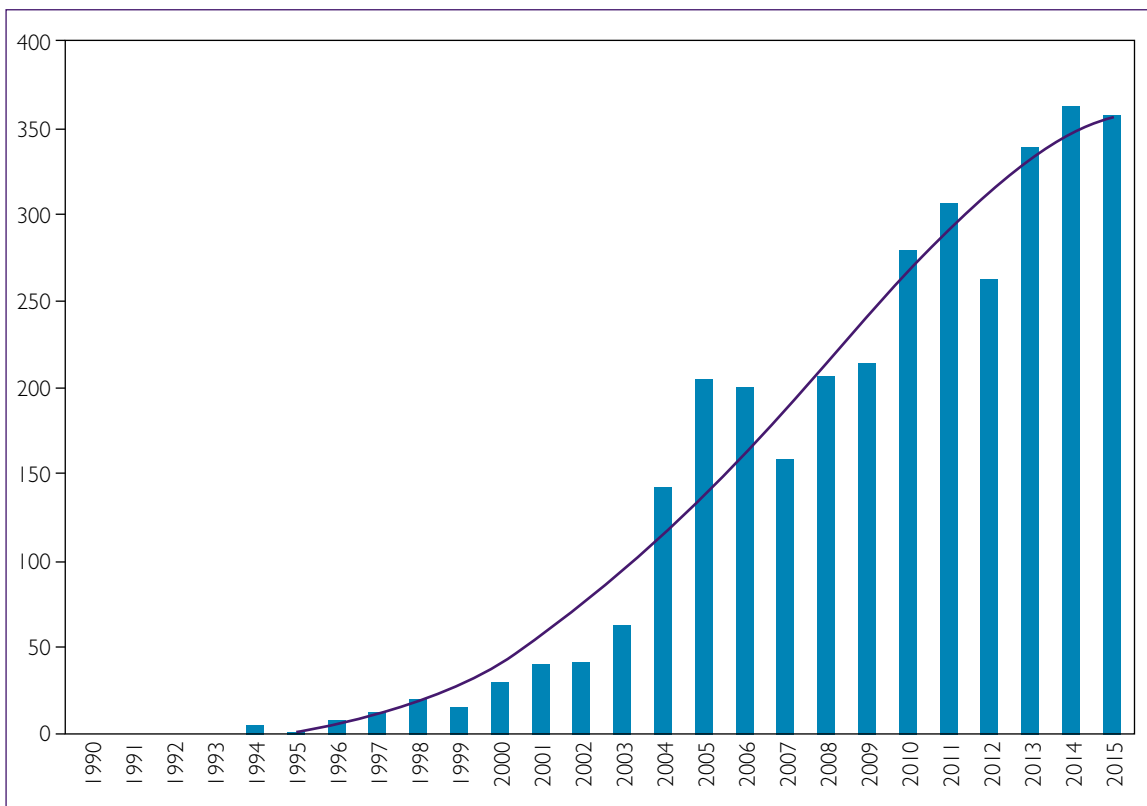
# Appendices

## Appendix I. (Number of search hits by search keywords (as of 31 December 2015))

Keyword	Number	%
'VAC'	1710	51.9%
'negative pressure wound therapy'	862	26.2%
'NPWT'	579	17.6%
'Vacuum assisted closure'	254	7.7%
'VAC therapy'	242	7.4%
'V.A.C.'	236	7.2%
'topical negative pressure'	230	7.0%
'vacuum sealing'	87	2.6%
'Topical negative pressure therapy'	72	2.2%
'V.A.C. therapy'	69	2.1%
'Vacuum dressing'	34	1.0%
'TNP therapy'	16	0.5%
'subatmospheric pressure therapy'	11	0.3%
'Vacuum sealing therapy'	3	0.1%
'Foam suction dressing'	2	0.1%
'Sealed surface wound suction'	0	0.0%

Note: two different keywords may produce the same search result. The total of the search results is thus higher than the number of citations (or 100%).

**Appendix 2.** Number of articles published on NPWT in peer-reviewed journals in the last two decades (red columns – number per year; the blue line represents the trendline). It should be noted that the last update was made on 31 December 2015



**Appendix 3** All randomised controlled studies describing clinical benefit for the patient (n=27, clear endpoint definition) and comparing NPWT versus 'standard therapy'. Literature search as of 31 December 2015

Year	Author/country/ journal	Group size/patient total/control group	Wound type (abbreviation)	Primary endpoint	
2000	McCallon et al/US /Ostomy Wound Manage	5+5 / 10 / saline-moistened gauze	Diabetic foot wounds (DFU)	Time to definitive closure	
2004	Jeschke et al/Germany/Plast Reconstr Surg	6+6 / 12 / conventional treatment group	Integra integration – Skin substitute fixation (SSF)	Integra take rate, period from Integra coverage to skin transplantation	
2004	Moisisidis et al/australia/Plast Reconstr Surg	10+10 / 20 / bolster dressing	Split-thickness skin graft fixation (STGS)	Epithelialisation and graft quality	
2006	Braakenburg et al/ Netherlands/Plast Reconstr Surg	33+32 / 65 / modern wound dressing	Acute and chronic wounds (ALL)	Wound ready for skin grafting or healing by secondary intention	
2006	Llanos et al/Chile/Ann Surg	30+30 - double-masked / 60 / Similar dressing but without connection to negative pressure	Integration of split- thickness skin grafts (STSG)	Loss of STSG, area at the fourth postoperative day	
2006	Vuerstaek et al/Netherlands /J Vasc Surg	30+30 / 60 / conventional wound care technique	Chronic lower leg ulcer (LLU)	Time to complete healing (days)	
2007	Armstrong et al/US/ Int Wound J	77+85 – Multicentre / 162 / conventional wound care technique	Diabetic foot amputation wound (DFU)	Wound size and healing	
2007	Moues et al/Netherlands / J Plast Reconstr Aesthet Surg	29+25 / 54 / Moist gauze therapy	Acute, traumatic, infected & chronic full-thickness wound (ALL)	Time needed to reach 'ready for surgical therapy'	

Follow-up in days	Significance level/tendency /confidence Intervals	Results/conclusions
ND	Positive tendency / no	Time to definitive closure in the NPWT group was achieved in 22.8 ( $\pm$ 17.4) days, compared with 42.8 ( $\pm$ 32.5) days in the control group.
24	0.003 / 0.002 / no	The take rate was 78 $\pm$ 8 percent in the conventional treatment group and 98 $\pm$ 2 percent in the fibrin/NPWT group ( $p$ <0.003).The mean period from Integra coverage to skin transplantation was 24 $\pm$ 3 days in the conventional treatment group but only 10 $\pm$ 1 days in the fibrin/negative-pressure therapy group ( $p$ <0.002). <i>'CONCLUSION: It is suggested that Integra be used in combination with fibrin glue and negative-pressure therapy to improve clinical outcomes and shorten hospital stays, with decreased risks of accompanying complications.'</i>
14	Positive tendency / $p$ <0.05 / no	At 2 weeks, wounds that received a NPWT had a greater degree of epithelialisation in six cases (30%), the same degree of epithelialisation in nine cases (45%), and less epithelialisation in five cases (25%) compared with their respective control wounds. Graft quality following NPWT was subjectively determined to be better in 10 cases (50 percent), equivalent in seven cases (35%), and worse in three cases (15%). Although the quantitative graft take was not significant, the qualitative graft take was found to be significantly better with the use of NPWT ( $p$ <0.05). <i>'CONCLUSION: Topical negative pressure significantly improved the qualitative appearance of split-thickness skin grafts as compared with standard bolster dressings.'</i>
nD	0, (positive tendency for patients with cardiovascular disease and/or diabetics) / no	The time to the primary endpoint with NPWT was not significantly shorter; except for patients with cardiovascular disease and/or diabetics. <i>'CONCLUSIONS: With NPWT, wound healing is at least as fast as with modern wound dressings. Especially cardiovascular and diabetic patients benefit from this therapy. The total costs of NPWT are comparable to those of modern wound dressings, but the advantage is its comfort for patients and nursing staff.'</i>
4	0,001 / no	The median loss of the STSG in the NPWT group was 0,0cm <sup>2</sup> versus 4,5cm <sup>2</sup> in the control group ( $p$ =0.001). <i>'CONCLUSIONS: The use of NPWT significantly diminishes the loss of STSG area, as well as shortens the days of hospital stay. Therefore, it should be routinely used for these kinds of procedures.'</i>
17	0,0001 / yes	The median time to complete healing was 29 days (95% confidence interval [CI]: 25.5 to 32.5) in the V.A.C. group compared with 45 days (95% CI: 36.2 to 53.8) in the control group ( $p$ =0.0001). <i>'CONCLUSIONS: NPWT therapy should be considered as the treatment of choice for chronic leg ulcers owing to its significant advantages in the time to complete healing and wound bed preparation time compared with conventional wound care. Particularly during the preparation stage, NPWT therapy appears to be superior to conventional wound care techniques.'</i>
112	a-0.03 / c-0.033 / no	Kaplan-Meier curves demonstrated statistically significantly faster healing in the NPWT group in both acute ( $p$ =0.030) and chronic wounds ( $p$ =0.033). <i>'CONCLUSIONS: In both the acute and the chronic wound groups, results for patients treated with NPWT were superior to those for the patients treated with SWT.'</i>
ND	Positive tendency / no	A tendency towards a shorter duration of therapy was found, which was most prominent in late-treated wounds. <i>'CONCLUSIONS: For the treatment of full-thickness wounds, vacuum therapy has proven to be a valid wound healing modality.'</i>

2008	Bee et al. / US / J Trauma	24+24 / 48 / Polyglactin mesh	Abdominal coverage after damage control laparotomy or abdominal compartment syndrome (COA)	Delayed primary fascial closure	
2008	Blume et al. / USA / Diabetes Care	169+166 – Multicenter / 342 / Advanced moist wound therapy (AMWT, predominately hydrogels and alginates)	Foot ulcers in diabetic patients (DFU)	Complete ulcer closure	
2008	Mody et al. / US / Ostomy Wound Manage	24+24 - blinded, prospective / 48 / Wet-to-dry gauze dressings	DFUs (15), PU (11), NF (11), and 'other' (11) (ALL)	Wound closure.	
2009	Stannard et al. / US / J Orthop Trauma	35+23 / 58 / Standard fine mesh gauze dressing	Open fractures with soft tissue defects – Extremity trauma wounds (ETW)	Deep wound infection or osteomyelitis, wound dehiscence	
2010	Chio et al. / USA / Otolaryngol Head Neck Surg	23+27 / 50 / Static pressure dressing	Integration of split-thickness skin grafts (STSG)	Area of graft failure	
2010	Perez et al. / Haiti / Am J Surg	20+20 / 40 / Conventional saline-soaked gauze dressing vs homemade wound vacuum-dressing system	Complex wounds in a resource-poor hospital (ALL)	Complete wound healing	
2010	Saaq et al. / Pakistan / J Coll Physicians Surg Pak	50+50 - single blinded / 100 / Normal saline gauzes	Pretreatment STSG, wound bed preparation (WBP)	Graft take, wound healing time	

nD	0 / no	There were no differences between delayed primary fascial closure rates in the VAC (31%) or MESH (26%) groups. <i>'CONCLUSIONS: MESH and NPWT are both useful methods for abdominal coverage, and are equally likely to produce delayed primary closure. The fistula rate for NPWT is most likely due to continued bowel manipulation with NPWT changes with a feeding tube in place-enteral feeds should be administered via nasojejunal tube. Neither method precludes secondary abdominal wall reconstruction.'</i>
112	0.007 / no	A greater proportion of foot ulcers achieved complete ulcer closure with NPWT (73 of 169, 43.2%) than with AMWT (48 of 166, 28.9%) within the 112-day active treatment phase (p=0.007). The Kaplan-Meier median estimate for 100% ulcer closure was 96 days (95% CI: 75.0–114.0) for NPWT and not determinable for AMWT (p=0.001). <i>'CONCLUSIONS: NPWT appears to be as safe as and more efficacious than AMWT for the treatment of diabetic foot ulcers.'</i>
70	0 / PU <0,05 / no	No statistically significant differences in time to closure between the two treatment groups were observed except in a subset analysis of pressure ulcers (mean 10 +/- 7.11 days for treatment and 27 +/- 10.6 days in control group, p=0.05). <i>'CONCLUSIONS: These results suggest that inexpensive materials can be utilized for NPWT wound closure in a developing country.'</i>
nd	0,024 / yes	Control patients developed 2 acute infections (8%) and 5 delayed infections (20%), for a total of 7 deep infections (28%), whereas NPWT patients developed 0 acute infections, 2 delayed infections (5.4%), for a total of 2 deep infections (5.4%). There is a significant difference between the groups for total infections (p=0.024). The relative risk ratio is 0.199 (95% confidence interval: 0.045-0.874), suggesting that patients treated with NPWT were only one-fifth as likely to have an infection compared with patients randomised to the control group. NPWT represents a promising new therapy for severe open fractures after high-energy trauma patients developed 2 acute infections (8%) and 5 delayed infections (20%), for a total of 7 deep infections (28%), whereas NPWT patients developed 0 acute infections, 2 delayed infections (5.4%), for a total of 2 deep infections (5.4%). There is a significant difference between the groups for total infections (p=0.024). <i>'CONCLUSION: The relative risk ratio is 0.199 (95% confidence interval: 0.045-0.874), suggesting that patients treated with NPWT were only one-fifth as likely to have an infection compared with patients randomized to the control group.'</i>
nD	0,361 / no	Percentage of area of graft failure between the groups also showed no difference (4.5% SPD versus 7.2% NPWT, P = 0.361). <i>'CONCLUSIONS: Although an attractive option for wound care, the NPWT does not appear to offer a significant improvement over an SPD in healing of the RFFF donor site.'</i>
25	0,013 / no	The time required to achieve complete healing was 16 days in the home made NPWT group compared with 25 days in the WET group (p=0.013). <i>'CONCLUSIONS: The homemade NPWT should be considered in underdeveloped countries to provide modern management for complex wounds because healing is significantly faster compared with conventional wound care. Although the HIM-VAC is more costly than the conventional approach, it is probably affordable for most resource-poor hospitals.'</i>
nD	Positive tendency / no	Marked differences were found in favour of the NPWT therapy group with respect to the various wound management outcome measures studied. i.e. graft take (greater than 95% graft take in 90% of NPWT therapy group versus 18% of controls), wound healing time (2 weeks postgrafting in 90% of NPWT therapy group vs. 18% of controls). <i>'CONCLUSION: NPWT therapy should be employed in the pre-treatment of wounds planned to be reconstructed with STSG, since it has marked advantages in the wound bed preparation compared with the traditional normal saline gauze dressings.'</i>

2011	Karatepe et al. / Turkey / Acta Chir Belg	30+37 / 67 / Standard wound care	Diabetic foot wound (DFU)	Healing time (time from hospital admission to the time of re-epithelisation)	
2011	Petkar et al. / India / Burns	21+19 / 40 / Conventional dressing consisting of Vaseline gauze & cotton pad	Skin graft in burns (STSG)	Amount of graft take, duration of dressings for the grafted area	
2012	Bloemen et al. / Netherlands / Wound Repair Regen	21+21+22+22 – Multicenter / 86 / With or without a dermal substitute and with or without NPWT	Skin graft in burns (STSG)	Graft take rate, graft quality	
2012	Liao et al. / China / Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi	30+30 / 60 / Conventional dressing	Skin graft (STSG)	Skin graft survival rate, graft quality	
2012	Serclova et al. / Czech Republic / Rozhl Chir	28+29 / 57 / Primary abdominal wall closure	Abdominal coverage after damage control laparotomy or abdominal compartment syndrome (COA)	Delayed primary fascial closure, mortality	
2013	Banasiewicz et al. / Poland / Pol Przegl Chir	10+9 / 19 / Standard wound dressing	Pilonidal sinuses (PSD)	Wound size, time of surgery, time of wound healing.	
2014	Biter et al. / Netherlands / Dis Colon Rectum	24+25 / 49 / Standard open wound care	Pilonidal sinus disease (PSD)	Time to complete wound healing.	



nD	< 0.05 / no	Healing time in the NPWT group was significantly reduced ( $p < 0.05$ ). All 8 domains of SF-36 and MCS and PCS scores improved remarkably after NPWT therapy. <i>'CONCLUSION: NPWT therapy was found to be effective in the treatment of chronic diabetic ulcers. The improvement of quality of life demonstrates a clear-cut indication in this particular group of patients.'</i>
II	< 0.001 / no	Final graft take at nine days in the study group ranged from 90–100% with an average of 96.7% (standard deviation: 3.55). The control group showed a graft take ranging between 70 and 100 percent with an average graft take of 87.5% (standard deviation: 8.73). Each of these differences was found to be statistically significant ( $p < 0.001$ ). <i>'CONCLUSION: Negative pressure dressing improves graft take in burns patients and can particularly be considered when wound bed and grafting conditions seem less-than-ideal. The negative pressure can also be effectively assembled using locally available materials thus significantly reducing the cost of treatment.'</i>
12 months	0 / significant better / no	Graft take and epithelialisation did not reveal significant differences. Highest elasticity was measured in scars treated with the substitute and TNP, which was significantly better compared to scars treated with the substitute alone. <i>'CONCLUSION: This randomized controlled trial shows the effectiveness of dermal substitution combined with NPWT in burns, based on extensive wound and scar measurements.'</i>
1-3 years	< 0.05 / < 0.05 / no	The skin graft survival rate, wound infection rate, reamputation rate, times of dressing change, and the hospitalization days in test group were significantly better than those in control group [90.0% versus 63.3%, 3.3% versus 20.0%, 0 versus 13.3%, (2.0±0.5) times vs. (8.0±1.5) times, and (12.0±2.6) days vs. (18.0±3.2) days, respectively] ( $p < 0.05$ ). At last follow-up, the scar area and grading, and two-point discrimination of wound in test group were better than those in control group, showing significant differences ( $p < 0.05$ ). <i>'CONCLUSION: Compared with direct anti-taken skin graft on amputation wound, the wound could be closed primarily by using the NPWT combined with anti-taken skin graft. At the same time it could achieve better wound drainage, reduce infection rate, promote good adhesion of wound, improve skin survival rate, and are beneficial to lower the amputation level, so it is an ideal way to deal with amputation wound in the phase I.'</i>
nD	DPFC < 0.01 / M < 0.01 / no	The mortality rate was significantly lower in the NPWT laparostomy group in comparison with the primary closure group (3 patients, 11% versus 12 patients, 41%; $p = 0.01$ ). A complete closure of the abdominal wall including fascia and complete abdominal wall healing was achieved in 80% of survivors in the NPWT group, compared to 29% in the primary closure group ( $p = 0.01$ ). <i>'CONCLUSIONS: Primary NPWT laparostomy is an effective and safe method in the treatment of severe peritonitis. Keeping good clinical practice, especially using dynamic suture as early as after the index surgery and the timely closure of laparostomy as soon as the indication disappears (according to relevant criteria) leads to a significantly higher abdominal wall healing rate, including fascial closure, than after peritonitis treatment without laparostomy.'</i>
nD	Positive tendency / no	In NPWT treated group the wound size and time of surgery were similar to control group. Time of wound healing, recovery and the pain after surgery in days 4-7 were reduced in comparison to the standard treated group. <i>'CONCLUSIONS: NPWT therapy can be easily used in an outpatient setting, mobile device is highly accepted, operation of the equipment is simple. NPWT therapy significantly decreases the time of wound healing and absenteeism from work as well as the postoperative late pain.'</i>
94	0.44 / no	Complete wound healing was achieved at a median of 84 days in the NPWT group versus 93 days in control patients ( $p = 0.44$ ). <i>'CONCLUSION: It is feasible to apply vacuum therapy in the treatment of pilonidal sinus disease, and it has a positive effect on wound size reduction in the first 2 weeks. However, there is no difference in time to complete wound healing and time to resume daily life activities.'</i>

2014	Kakagia et al. / Greece / Injury	42+40 / 82 / Shoelace technique	Leg fasciotomy wound (ETW)	Time to definite closure	
2014	Lone et al. / India / Diabet Foot Ankle	28+28 / 56 / Conventional dressing	DFU	Time to prepare the wound for closure either spontaneously or by surgery	
2014	Monsen et al. / Sweden / J Vasc Surg	10+10 / 20 / Alginate therapy	Deep perivascular groin wound infection after vascular surgery (Szilagyi grade III) (PGI)	Time to full skin epithelialisation	
2015	Kirkpatrick et al. / Canada / Ann Surg	23+22 / 45 / Barker's vacuum pack	Abdominal sepsis (COA)	Delayed primary fascial closure (DPFC), Mortality	
2015	Rencuzogullari et al. / Turkey / Ulus Travma Acil Cerrahi Derg	20+20 / 40 / Bogota bag technique	Open abdomen, abdominal sepsis (COA)	Delayed primary fascial closure (DPFC), Mortality	

7	! minus 0,001 / no	Wound closure time was significantly higher in NPWT group compared to control group (p=0.001; 95% CI of the difference: 1.8–6.3 days). <i>'CONCLUSIONS: Both NPWT and the shoelace technique are safe, reliable and effective methods for closure of leg fasciotomy wounds. NPWT requires longer time to definite wound closure and is far more expensive than the shoelace technique, especially when additional skin grafting is required.'</i>
42	+ / no	Granulation tissue appeared in 26 (92.85%) patients by the end of week 2 in NPWT group, while it appeared in 15 (53.57%) patients by that time in control group. 100% granulation was achieved in 21 (77.78%) patients by the end of week 5 in NPWT group as compared with only 10 (40%) patients by that time in control group. <i>'CONCLUSION: NPWT appears to be more effective, safe, and patient satisfactory compared to conventional dressings for the treatment of DFUs.'</i>
104	0.026 / no	Time to full skin epithelialisation was significantly shorter in the NPWT group (median, 57 days) compared with the alginate group (median, 104 days; p=0.026). <i>'CONCLUSIONS: NPWT achieves faster healing than alginate therapy after wound debridement for deep perivascular wound infections in the groin after vascular surgery. This finding does not allow further inclusion of patients from an ethical point of view, and this study was, therefore, stopped prematurely'</i>
90	DPFC-0.17 / M-0.04 / no	The cumulative incidence of primary fascial closure at 90 days was similar between groups (hazard ratio, 1.6; 95% CI: 0.82–3.0, p=0.17). However, 90-day mortality was improved in the NPWT group (hazard ratio, 0.32; 95% confidence interval, 0.11–0.93; p=0.04). <i>'CONCLUSIONS: This trial observed a survival difference between patients randomized to the NPWT versus Barker's vacuum pack that did not seem to be mediated by an improvement in peritoneal fluid drainage, fascial closure rates, or markers of systemic inflammation.'</i>
nD	DPFC-+ / M-+ / no	Primary closure of fascia was considered appropriate in 16.9 days in the NPWT group and 20.5 days in the Bogota bag group. 12 patients (30%) died during the study. Among the deceased patients, 5 (12%) were in the NPWT group, whereas, 7 (17.5%) belonged to the Bogota bag group. <i>'CONCLUSION: Based on these results, it is suggested that VAC has advantages when compared to the Bogota bag as a temporary closure method in the management of abdominal compartment syndrome.'</i>

**Appendix 4. TOP 20 journals publishing peer-reviewed articles dealing with NPWT (Literature search as of 31 Decemeber 2015) Impact factor according to (2013)**

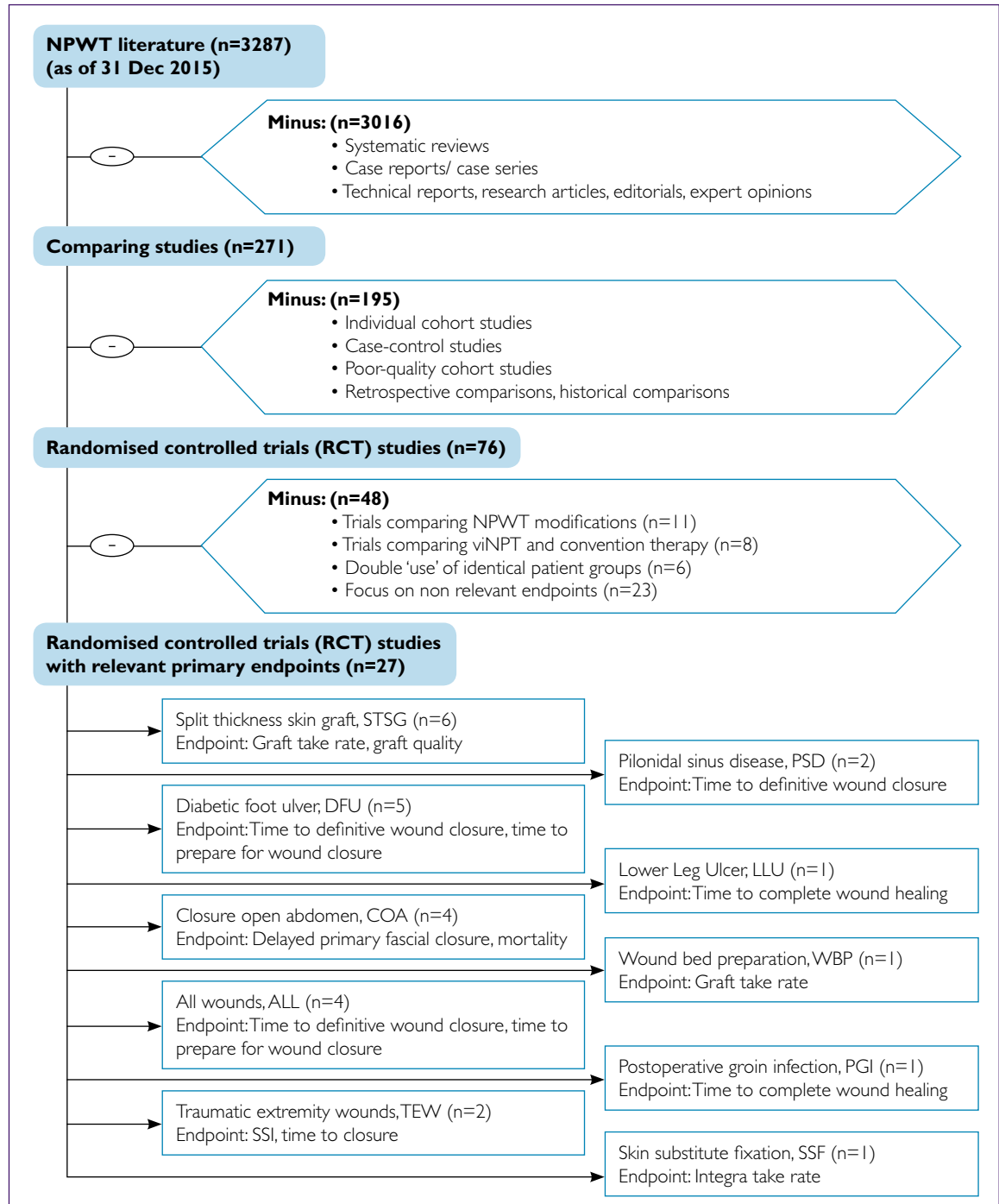
Rank	Journal	Number	Impact Factor
1	Int Wound J	181	2.150
2	Zentralbl Chir	116	1.048
3	J Wound Care	113	1.069
4	Plast Reconstr Surg	102	2.993
5	Ostomy Wound Manage	87	1.122
6	Ann Plast Surg	74	1.494
7	J Plast Reconstr Aesthet Surg	74	1.421
8	Wound Repair Regen	57	2.745
9	Interact Cardiovasc Thorac Surg	55	1.155
10	Ann Thorac Surg	53	3.849
11	Wounds	38	0.538
12	J Wound Ostomy Continence Nurs	36	1.177
13	J Trauma	33	2.961
14	Int J Low Extrem Wounds	33	0.928
15	J Orthop Trauma	31	1.803
16	Adv Skin Wound Care	30	1.106
17	Eplasty	26	0.000
18	Eur J Cardiothorac Surg	24	3.304
19	Am Surg	23	0.818
20	Am J Surg	22	2.291

**Appendix 5. Number of publications for the various evidence levels dealing with ‘NPWT’ (titles and any field) according to the Oxford Centre for Evidence-Based Medicine (Oxford CEBM). Literature search as of 31 December 2015**

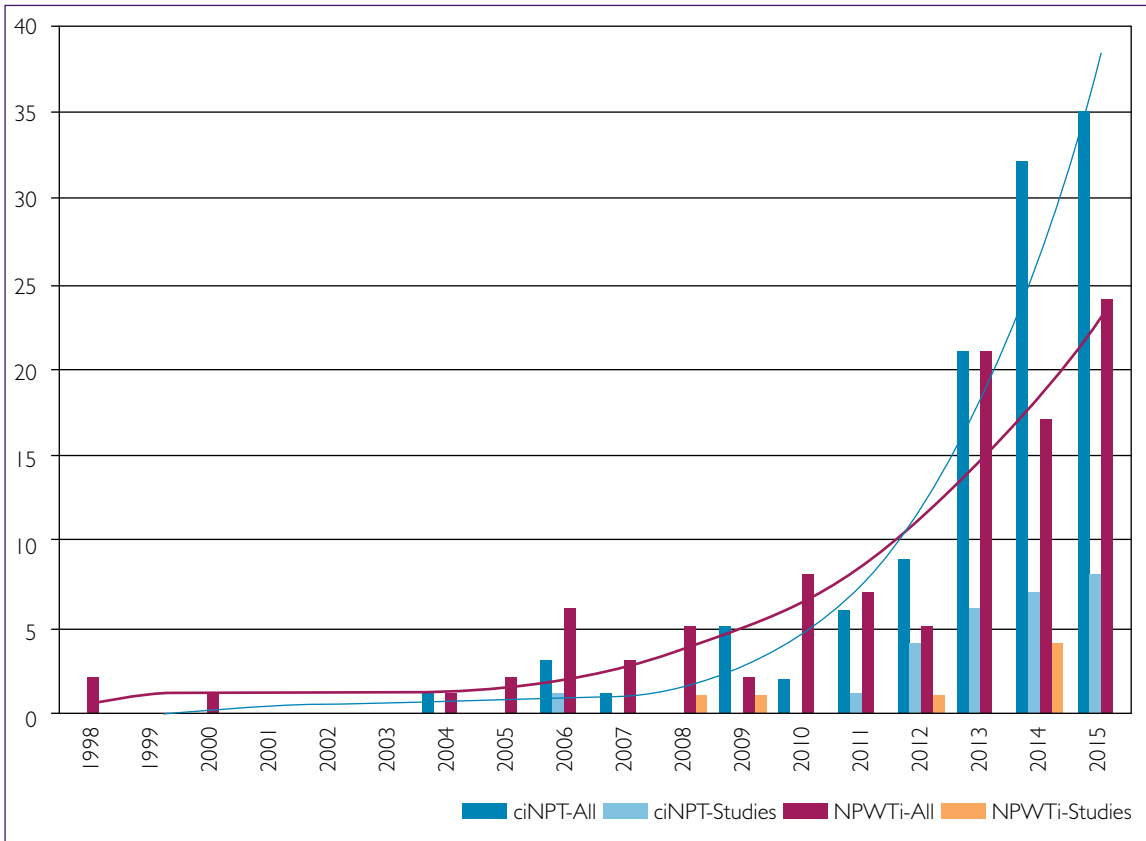
Evidence Level	Therapy / Prevention, Risks / Side-Effects	Number (%)
1a	Systematic review (with homogeneity) of RCTs	6 (0.2%)
1b	Individual RCT (with narrow confidence interval, group size > 20 pts)	38 (1.2%)
1c	All or none*	0
2a	Systematic review (with homogeneity) of cohort studies	7 (0.2%)
2b	Individual cohort study (incl. low quality RCT, e.g. follow-up < 80%)	78 (2.4%)
2c	‘Outcomes’ research, ecological study	0
3a	Systematic review (with homogeneity) of case-control studies	55 (1.7%)
3b	Individual case-control studies	13 (0.4%)
4	Case series (and poor-quality cohort studies and poor case-control studies), retrospective studies, historical comparison	73 (2.2%)
4 / 5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or ‘first principles’	2778 (84.5%)
. - .	Technical reports, research articles	239 (7.3)

Adapted to the Classification by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes (March 2009)<sup>1</sup>; \*e.g. when all patients died before the therapy became available, but some now survive on it, or when some patients died, but none now die on it.

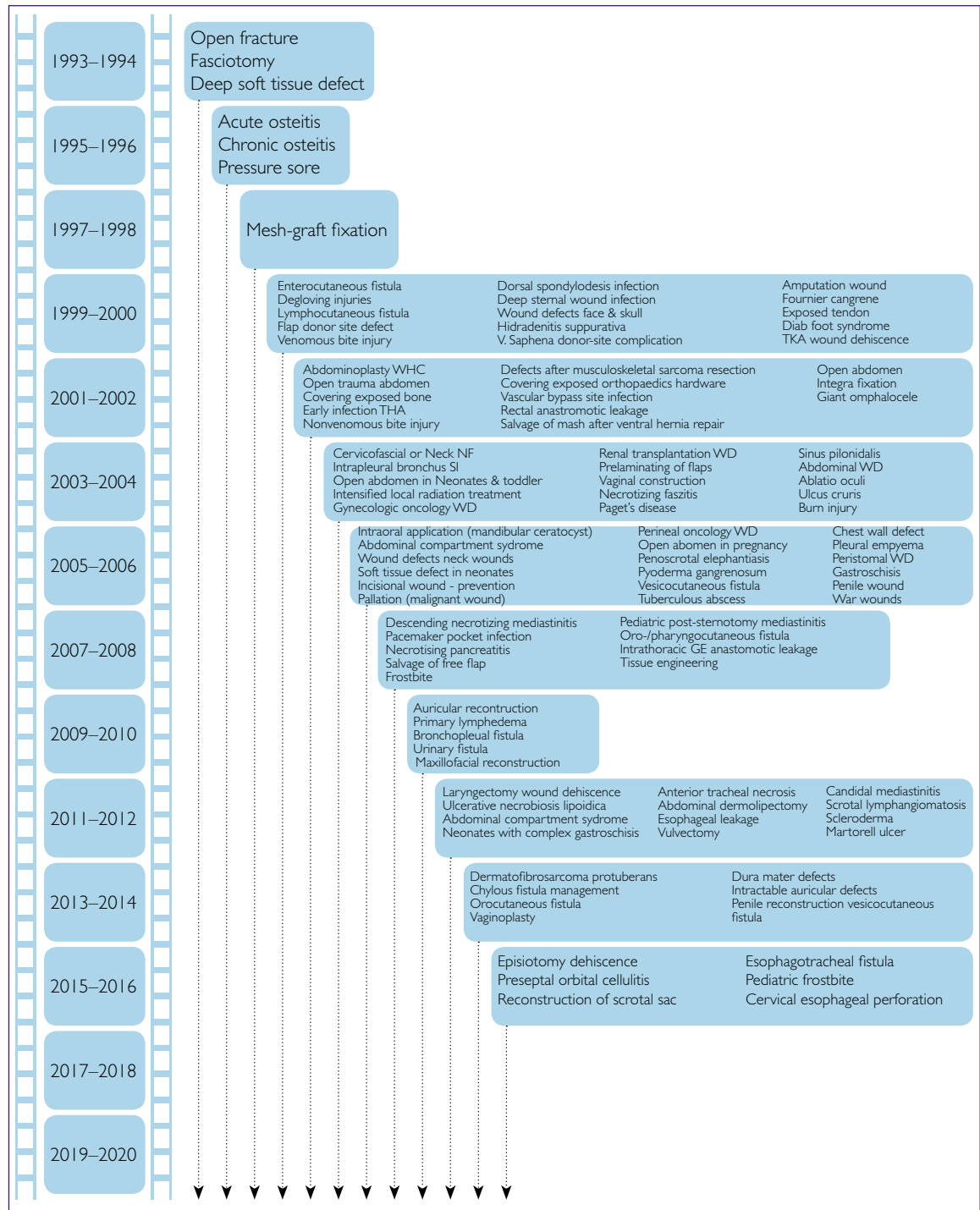
**Appendix 6.** Flow chart (papers identified n=3287, RCTs with clearly defined endpoints n=27)



**Appendix 7.** Number of articles published on (closed incisional negative pressure treatment (ciNPT) und negative pressure wound therapy and instillation (NPWTi) in peer-reviewed journals in the last two decades (blue columns – number per year for ciNPT literature (bright blue portion of comparing trials in absolute numbers, blue line = trendline), the red columns – number per year for NPWTi literature (bright red portion of comparing trials in absolute numbers, red line = trendline). Based on literature research as of 31 December 2015



**Appendix 8. Development of the spectrum of indications up to 2015. The assigned time is based on the date of publication**







## Appendix 9. Comparative studies 'standard wound therapy' versus NPWTi and NPWT versus NPWTi

Year	Author / Country / Journal	Study/Evidence-level	Group size	Modus of instillation	
2008	Gabriel et al. / US / Int Wound J	Retrospective control group - low quality / 4	15 NPWTi + 15 (standard moist wound-care therapy)	Polyhexanide	
2009	Timmers et al. / Netherlands / Wound Repair Regen	Retrospective case-control cohort study / 4	30+94 (implantation of gentamicin polymethylmethacrylate beads and long-term intravenous antibiotics)	Irrigation through the tubes three times a day with a polyhexanide antiseptic solution	
2012	Goss et al. / US / J Am Coll Clin Wound Spec	Prospective pilot study - Cohort study - low quality / 4	n=8: Sharp surgical debridement followed by NPWTi versus n=8: Standard algorithm (sharp surgical debridement followed by NPWT)	NPWTi with quarter strength bleach solution	
2014	Gabriel et al. / US / Eplasty	Retrospective analysis cohort study / 3b; hypothetical economic model using cost assumptions	34 (NPWT) +48 (NPWTi)	Fluid: saline or polyhexanide	
2014	Kim et al. / US / Plast Reconstr Surg	Retrospective, historical, cohort-control study - low quality / 4	NPWT: n = 74; NPWTi: n = 34, dwell time 6 min, n=33, dwell time n=20 minutes	With and without instillation	

	Wounds	Endpoints	Results/conclusions
	Complex, infected wounds	Days of treatment, Reduction of infection, wound closure, in-hospital stay	NPWT-instillation group required fewer days of treatment (36.5±13.1 versus 9.9±4.3 days, p<0.001), cleared of clinical infection earlier (25.9 +/- 6.6 versus 6.0±1.5 days, p<0.001), had wounds close earlier (29.6±6.5 versus 13.2±6.8 days, p<0.001) and had fewer in-hospital stay days (39.2±12.1 versus 14.7±9.2 days, p<0.001). <i>CONCLUSION: 'The use of NPWT instillation may reduce cost and decrease inpatient care requirements for these complex, infected wounds.'</i>
	Posttraumatic osteomyelitis after surgical debridement	Time to wound closure, number of surgical procedures, recurrence of infection	NPWTi: Rate of recurrence of infection was 3/30 (10%), 55/93 (58.5%) of the controls had a recurrence (p<0.0001). NPWTi: Total duration of hospital stay was shorter and number of surgical procedures smaller as compared with the controls (all p<0.0001). <i>CONCLUSION: '... in posttraumatic osteomyelitis negative pressure instillation therapy reduces the need for repeated surgical interventions in comparison with the present standard approach.'</i>
	Contaminated chronic lower leg and foot wounds	Efficacy of wound bed preparation, CFU/gram tissue culture	The mean CFU/gram tissue culture was statistically greater - $3.7 \times 10^6$ ( $\pm 4 \times 10^6$ ) in the NPWTi group, while in the standard group (NPWT) the mean was $1.8 \times 10^6$ ( $\pm 2.36 \times 10^6$ ) CFU/gram tissue culture (p=0.016). The mean absolute reduction in bacteria for the NPWTi group was $10.6 \times 10^6$ bacteria per gram of tissue while there was a mean absolute increase in bacteria for the NPWT group of $28.7 \times 10^6$ bacteria per gram of tissue, therefore there was a statistically significant reduction in the absolute bioburden in those wounds treated with NPWTi (p=0.016). <i>CONCLUSION: 'Wounds treated with NPWTi (in this case with quarter strength bleach instillation solution) had a statistically significant reduction in bioburden, while wounds treated with NPWT had an increase in bioburden over the 7 days.'</i>
	Extremity and trunk wounds	Clinical outcomes, cost-differences	RESULTS showed significant differences (p<0.0001) between NPWTi-d and NPWT patients, respectively, for the following: mean operating room debridements (2.0 versus 4.4), mean hospital stay (8.1 versus 27.4 days), mean length of therapy (4.1 versus 20.9 days), and mean time to wound closure (4.1 versus 20.9 days). Hypothetical economic model showed potential average reduction of \$8143 for operating room debridements between NPWTi-d (\$6786) and NPWT (\$14,929) patients. <i>CONCLUSION: '... NPWTi-d appeared to assist in wound cleansing and exudate removal, which may have allowed for earlier wound closure compared to NPWT. Hypothetical economic model findings illustrate potential cost-effectiveness of NPWTi-d compared to NPWT.'</i>
	Acutely and chronically infected wounds	Time to final surgical procedure, hospital stay, number of operative visits	Number of operative visits was significantly lower for the 6- and 20-minute dwell time groups (2.4±0.9 and 2.6±0.9, respectively) compared with the no-instillation group (3.0±0.9) (p≤0.05). Hospital stay was significantly shorter for the 20-minute dwell time group (11.4±5.1 days) compared with the no-instillation group (14.92±9.23 days) (p≤0.05). Time to final surgical procedure was significantly shorter for the 6- and 20-minute dwell time groups (7.8±5.2 and 7.5±3.1 days, respectively) compared with the no-instillation group (9.23±5.2 days) (p≤0.05). Percentage of wounds closed before discharge and culture improvement for Gram-positive bacteria was significantly higher for the 6-minute dwell time group (94 and 90%, respectively) compared with the no-instillation group (62 and 63%, respectively) (p≤0.05). <i>CONCLUSION: 'NPWTi (6- or 20-minute dwell time) is more beneficial than standard NPWT for the adjunctive treatment of acutely and chronically infected wounds ...'</i>

2014	Tao et al. / China / Gastroenterol Res Pract	Retrospective cohort study - low quality / 4	NPWT mesh-mediated fascial traction and (n=73). NPWTi: n=61	nD	
2015	Kim et al. / US / Plast Reconstr Surg	Prospektive randomized controlled trial / 2b	n= 123	Comparing 0.9% normal saline versus 0.1% polyhexanide plus 0.1% betaine	
2015	Sun et al. / China / Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi	Prospektive randomized controlled trial / 2b	NPWT (A, n = 11) NPWTi + saline (B, n = 11) , NPWTi + unsulin solution (C, n = 12)	Comparing 0.9% normal saline versus insulin solution	
2015	Wen et al. / China / Zhonghua Shao Shang Za Zhi	Prospektive randomized controlled trial / 2b	NPWT (A, n=11) NPWTi + saline (B, n = 11) , NPWTi + oxygen loaded fluid irrigation (C, n = 12)	Comparing 0.9% normal saline versus oxygen loaded fluid	

	Open Septic Abdomen	Rate of delayed primary fascial closure (DPFC)	The DPFC rate in the instillation group was significantly increased (63% versus 41%, $p=0.011$ ). The mortality with OA was similar (24.6% versus 23%, $p=0.817$ ) between the two groups. However, time to DPFC ( $p=0.003$ ) and length of stay in hospital ( $p=0.022$ ) of the survivals were significantly decreased in the instillation group. In addition, NPWT-instillation (OR: 1.453, 95%CI: 1.222-4.927, $p=0.011$ ) was an independent influencing factor related to successful DPFC. <i>CONCLUSION: 'VAWCM-instillation could improve the DPFC rate but could not decrease the mortality in the patients with open septic abdomen.'</i>
	Infected wounds that required hospital admission and operative debridement.	Number of operative visits, length of hospital stay, time to final surgical procedure, proportion of closed or covered wounds, and proportion of wounds that remained closed or covered at the 30-day follow-up	There was no statistically significant difference in the surrogate outcomes with the exception of the time to final surgical procedure favoring normal saline ( $p=0.038$ ). <i>CONCLUSION: '0.9% normal saline may be as effective as an antiseptic (0.1% polyhexanide plus 0.1% betaine) for negative-pressure wound therapy with instillation for the adjunctive inpatient management of infected wounds.'</i>
	Chronic diabetic lower limb ulcer	Concentration of insulin growth factor I (IGF-I), tumor growth factor $\alpha$ (TNF- $\alpha$ ), nitric oxide (NO) in necrotic tissue. Coverage rate, thickness of granulation tissue, clearance rate of bacteria, histology of granulation tissue (HE staining) after 6 days of treatment	HE staining: few new microvessels and fibroblasts in group A after treatment; more new microvessels and fibroblasts were observed in group B; and many new microvessels and fibroblasts were found in group C. Coverage rate / thickness of granulation tissue and clearance rate of bacteria in group C were significantly higher ( $p<0.05$ ). IGF-I and NO significantly increased and TNF- $\alpha$ significantly decreased in group C when compared with those in group A ( $p<0.05$ ). Compared with group B, IGF-I and NO contents were significantly increased at 3-6 days and at 2-6 days respectively, and TNF- $\alpha$ content was significantly decreased at 3-6 days in group C ( $p<0.05$ ). Time second stage operation in group C was significantly shorter than that in groups A and B ( $p<0.05$ ). Survival rate of grafted skin or flap in group C was significantly higher than that in groups A and B ( $p<0.05$ ). <i>CONCLUSION: 'Treatment of diabetic lower limb ulcers with ... irrigation of insulin solution combined with NPWTi can reduce inflammatory reaction effectively, promote development of granulation tissue, improve recovery function of tissue, increase the rate and speed of wound healing obviously, but it has no effect on blood glucose levels.'</i>
	Chronic venous leg ulcer	Granulation tissue coverage rate, amount new born microvessels and fibroblasts, fresh collagen, $pO_2$ skin, Expression of VECF, number of type I + II macrophages in granulation tissue	Granulation tissue coverage rate of wounds in patients of group C was higher than that of group A or B ( $p<0.05$ or $p<0.01$ ). HE staining: more abundant new born microvessels and fibroblasts in group C; Masson staining: more abundant fresh collagen distributed orderly, $pO_2$ skin around the wounds in patients of group C significant higher ( $p < 0.01$ ). Expression of VECF in the wounds of patients in group C was higher than that in group A or B ( $p<0.05$ or $p<0.01$ ). On PTD 7, the number of type I macrophages in granulation tissue of patients was respectively $14.3 \pm 2.3$ , $11.5 \pm 3.0$ , and $10.7 \pm 2.3$ per 400 times vision field in groups A, B, and C ( $F=25.14$ , $p<0.01$ ), while the number in group C was less than that in group A or B ( $p<0.05$ or $p<0.01$ ). On PTD 7, the number of type II macrophages in granulation tissue of patients was respectively $32.7 \pm 3.2$ , $35.1 \pm 3.3$ , and $41.3 \pm 3.2$ per 400 times vision field in groups A, B, and C ( $F=81.10$ , $p<0.01$ ), and the number in group C was larger than that in group A or B ( $p<0.01$ ). <i>CONCLUSIONS: 'NPWT combined with irrigation of oxygen loaded fluid can raise the <math>pO_2</math>-skin around the wounds effectively, promoting the transition of macrophages from type I to type II, thus it may promote the growth of granulation tissue, resulting in a better recipient for skin grafting or epithelisation.'</i>

## Appendix 10. Overview of all published randomised controlled trials and meta-analyses dealing with ciNPT in all surgical fields

Year	Author / journal	EBM-Level*	Number of patients/study design	
2015	Scalise et al. / Italy / Int Wound J	Ia (systematic review, meta-analysis of RCT's, other comparative studies)	1 biomedical engineering study, 2 animal studies, 15 human studies for a total of 6 randomized controlled trials, 5 prospective cohort studies, 7 retrospective analyses, were included	
2015	Semsarzadeh et al. / USA / Plast Reconstr Surg	Ia (systematic review, meta-analysis of RCT's, other comparative studies)	n=8 studies implemented (based on a search for experimental and epidemiological study designs, including randomized controlled trials, pseudo-randomized trials, quasi-experimental studies, before and after studies, prospective and retrospective cohort studies, case control studies, and analytical cross sectional studies	
2015	Sandy-Hodgetts et al. / Australia / JBI Database System Rev Implement Rep	Ia (systematic review, meta-analysis of RCT's, other comparative studies)	n=8 studies implemented (based on a search for experimental and epidemiological study designs, including randomized controlled trials, pseudo-randomized trials, quasi-experimental studies, before and after studies, prospective and retrospective cohort studies, case control studies, and analytical cross sectional studies	
2015	Gillespie et al. / Australia / Surg Innov	Ib (nonmasked, randomized controlled pilot trial)	Group A: ciNPT, n=35 Group B: Control, n=35, standard care hydrocolloid & 2 absorbent dressings; Follow up: 6 weeks	
2014	Webster et al. / Australia / Cochrane Database Syst Rev	Ia (meta-analysis of RCT's, other comparative studies)	Meta-analysis	
2013	Ingargiola et al. / USA / Eplasty	Ia (databases from 2006 to 2012 for published articles (meta-analysis of RCT's, other comparative studies)	Meta-analysis	

	Type of wounds	Primary outcome/results	Conclusion/comment
	All type of wounds	Decrease in the incidence of infection, sero-haematoma formation and of the re-operation rates when using ciNPT. Lower level of evidence was found on dehiscence: decreased in some studies.	Because of limited studies, it is difficult to make any assertions on the other variables, suggesting a requirement for further studies for proper recommendations on iNPWT.
	All type of wounds	The overall weighted average rates of SSI in the ciNPT and control groups were 6.61% and 9.36%, respectively. This reflects a relative reduction in SSI rate of 29.4%. A decreased likelihood of SSI was evident in the ciNPT group compared with the control group across all studies, and across all four incision location subgroups. Overall rates of dehiscence in ciNPT and control groups were 5.32% and 10.68%, respectively.	ciNPT is a potentially effective method for reducing SSI. It also appears that ciNPT may be associated with a decreased incidence of dehiscence, but the published data available were too heterogeneous to perform meta-analysis.
	Trauma, cardiothoracic, orthopedic, abdominal, or vascular surgery	Endpoints: Occurrence of SSI or dehiscence as measured by the following: SSI - superficial and deep; surgical wound dehiscence; wound pain; wound seroma; wound hematoma. Statistically significant difference in favor of the use of ciNPT as compared to standard surgical dressings was found for SSI.	Demonstrated association between the use of ciNPT and reduction in SSI.
	Elective hip arthroplasty	Endpoints: Postoperative complications (SSI, length of stay, readmission) and skin complications (bruising, seroma, hematoma, dehiscence) SSI incidence was 2/35 in group A, 3/35 in group B [RR = 0.67; 95% CI: 0.12–3.7; p=0.65]. ciNPT patients experienced more postoperative wound complications [RR: 1.6; 95% CI: 1.0–2.5; p=0.04].	'A reduction of 3% in SSI incidence suggests that a definitive trial requires approximately 900 patients per group. Yet there is uncertainty around the benefit of NPWT after elective hip arthroplasty.'
	3 trials involved skin grafts, 4 included orthopaedic patients and 2 included general surgery and trauma surgery patients	Evidence for the effects of ciNPT for reducing SSI and wound dehiscence remains unclear; as does the effect of ciNPT on time to complete healing.	Urgent need for suitably powered, high-quality trials to evaluate the effects ciNPT. Such trials should focus initially on wounds that may be difficult to heal, such as sternal wounds or incisions on obese patients.
	All type of wounds	Literature shows a significant decrease in rates of infection when using ciNPT. Results inconsistent to formulate a clear statement. Because of limited studies, it is difficult to make any assertions on seroma, hematoma, and skin necrosis.	Possible evidence of a decrease in the incidence of infection with application of ciNPT. Looking at other variables such as dehiscence, seroma, hematoma, and skin necrosis show no consistent data and suggest further studies in order for proper recommendations for ciNPT.

2012	Stannard et al. / USA / J Orthop Trauma	Ib (Prospective randomized multicenter clinical trial)	Group A: ciNPT, n=141 Group B: Control, n=122, standard postoperative dressings; Follow up 6 weeks	
2012	Masden et al. / USA / Ann Surg	Ib (randomized controlled trial)	Group A: ciNPT, n=44 Group B: Control, n=37, standard postoperative dressings; Average follow-up was 113 days	
2011	Howell et al. / USA / Current Orthopaedic Practice	Ib (randomized controlled trial)	Group A: ciNPT, n=24 Group B: Control, n=36, sterile gauze; Average follow-up was 113 days	
2009	Stannard et al. / USA / J Orthop Trauma	Ib (randomized controlled trial)	Group A: ciNPT, n=35 Group B: Control, n=23, fine mesh gauze dressing; Average follow-up was 113 days	
<p>*Classification produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes (March 2009);<sup>1</sup> Wound healing problems—wound dehiscence, eschar, or drainage over three weeks post surgery; ‡Significant wound complications = wound complications that require surgical intervention; BMI—body mass index; ciNPT—closed incision negative pressure therapy; OR—odds ratio; CI—confidence interval; ciNPT—closed incision negative pressure therapy; SSI—Surgical site infection</p>				



Blunt trauma patients with one of three high-risk fracture types (tibial plateau, pilon, calcaneus) requiring surgical stabilization	There were a total of 23 infections in Group B and 14 in Group A, which represented a significant difference in favor of ciNPT (p=0.049). The relative risk of developing an SSI was 1.9 times higher in control patients than in patients treated with ciNPT (95% CI: 1.03–3.55). Decreased incidence of wound dehiscence and SSI after high-risk fractures when patients have ciNPT.	There have been no studies evaluating ciNPT as a prophylactic treatment to prevent SSI and wound dehiscence of high-risk surgical incisions up to 2012. ciNPT should be considered for high-risk wounds after severe skeletal trauma.
Mostly lower extremity wound closure	6.8% of the ciNPT group and 13.5% of the dry dressing group developed SSI - not statistically significant (p=0.46). No difference in time to develop infection. No statistical difference in dehiscence between ciNPT and dry dressing group (36.4% versus 29.7%; p=0.54) or mean time to dehiscence (p=0.45). Overall, 35% of the dry dressing group and 40% of the ciNPT group had a SSI, dehiscence, or both. Of these, 9 in the ciNPT group (21%) and 8 in the dry dressing group (22%) required reoperation.	No difference in the incidence of SSI or dehiscence between the ciNPT and dry dressing group.
Total Knee Replacement procedures & BMI > 30	No significant difference of days to a dry wound (4.3 days ciNPT, 4.1 days sterile gauze). There were 2 SSI, one in each arm of the study. Study was stopped prematurely when 15 of 24 knees (63%) treated with ciNPT developed skin blisters.	ciNPT did not appear to hasten wound closure and was associated with blisters. There does not appear to be a benefit to the routine use of ciNPT in the immediate postoperative TKA period.
Severe open fractures	Control patients developed 2 SSI (8%) and 5 delayed infections (20%), for a total of 7 deep infections (28%), whereas ciNPT patients developed 0 acute infections, 2 delayed infections (5.4%), for a total of 2 deep infections (5.4%). Significant difference between groups for total infections (p=0.024). The relative risk ratio is 0.199 (95% confidence interval: 0.045-0.874).	ciNPT represents a promising new therapy for severe open fractures after high-energy trauma suggesting that patients treated with ciNPT were only one-fifth as likely to have an infection compared with patients randomized to the control group.

## Appendix II. Reimbursement situation in selected EU countries (2016 data)

Country	Reimbursement	Bought/leased	
<b>FRANCE</b>	<b>No specific reimbursement</b> No specific funding (DRG funding) Private health insurance are not funding either.	<b>No specific reimbursement</b> All acquisition or leasing are part of the DRG funding. However, companies are implementing free leasing with higher consumable prices.	
<b>GERMANY</b>	<b>Yes</b> Within the hospital setting	<b>Both</b>	
<b>ITALY</b>	<b>No reimbursement</b> It is considered part of other procedures. This is up to a single hospital budget	<b>Both</b> Although not reimbursed, where used it gets a fee per day /dressing change reimbursement	
<b>SPAIN</b>	<b>No</b> No national reimbursement. Both public and private settings acquire NPWT products through direct purchasing. In the public sector, if purchases are above 18K €/year per code of product, they normally proceed through Public Tender (at a Hospital Level normally; still rarely at Regional level due to lack of homogeneity in the use/demand)	<b>Both</b> NPWT devices are leased (customer buys just the fungibles), except single use devices (everything bought). Some private hospitals and insurance companies prefer to pay a forfeit (cost per day), to get the service on demand.	
<b>UK</b>	<b>Yes</b> In hospital - NPWT is paid for by NHS (devices and consumables). The amount or time that NPWT is provided for depends on the individual hospital and the budget they have available. An NPWT tariff does exist for reimbursement but is rarely used.	<b>Both</b> Hospitals choose the best business model to suit their needs and budgets.	

	Home care	Training	Protocols
	<p><b>No specific reimbursement</b> NPWT is restricted to hospital and Home care through Hospitalization at Home (HAD). The reimbursement however is not specific to NPWT and may be considered similar to DRG. Community care is not considered as an indication in the recommendations of the HAS</p>	<p><b>Yes</b> A specific training is required by the HAS recommendations for NPWT The company and the hospitals are providing training, (company provide training to hospital, hospital provide training to patient)</p>	<p><b>Yes</b> But no national protocol, except a part within the recommendations of the HAS underlining the place of NPWT in the strategy (first-second line). Regional and local protocols may be available, and developed according to the situation The company provides protocols based on the cicatrisation step</p>
	<p><b>No</b> Not in general reimbursed, just on a case by case decision depending on the SHI company</p>	<p><b>Yes</b> Provided by company</p>	<p><b>No</b> No protocols exists</p>
	<p><b>Yes/no</b> Some exceptions are considered in Piemonte, Sicily, Tuscany and Lombardy for home care /outpatient treatments</p>	<p><b>Yes</b> Always by company</p>	<p><b>Yes</b> In some areas: Emilia and Tuscany. Protocols are provided by specific experts/clinicians chosen by regional healthcare administrations</p>
	<p><b>Yes/No</b> Not very often, but it occurs in some hospitals, mainly through portable or single use devices. The limitation for this use is not strictly due to budget constrictions, but to the lack of penetration of the use of NPWT in Spain, compared to conventional wound dressings</p>	<p><b>Yes</b> Almost always provided by companies (mainly in hospital, but also during conferences)</p>	<p><b>Yes</b> At hospital level, but not always: it depends on each one's requirements. There is not a clear consensus nor assumption of the use at a national level yet, so it is not a must to having a protocol to use NPWT (big part of the use remains on individual decisions, case by case). Protocols are normally provided by companies in first instance (based in evidence/consensus), and afterwards adopted and adapted by customers in regards to their characteristics/needs.</p>
	<p><b>Yes/no</b> Consumables are reimbursed via UK Drug Tariff but Multi patient use devices are not. Single patient use NPWT is reimbursed on UK Drug Tariff.</p>	<p><b>Yes</b> Training is provided by expert clinicians as well as the company. Not reimbursed.</p>	<p><b>Yes</b> Lead clinicians in each individual facility decide and put in place local protocols.</p>

## Appendix 12. Comparative studies—health economics

Author	Year	Country	Type of study	Study population	Intervention	
Apelqvist, J., et al.	2008	USA (and Sweden)	RCT	162 patients	Patients with post-amputation wounds due to diabetic foot treated with VAC and standard MWT	
Aydin, U., et al.	2015	Turkey	Cohort	21 patients	Various treatments for lymphocele or lymphorrhea	
Baharestani, M. M., et al.	2008	USA	Cohort	562 patients	Early vs. late initiation of NPWT in treating pressure ulcers and surgical wounds	
Braakenburg A., et al.	2006	The Netherlands	RCT	65 patients	VAC and conventional therapy	
De Leon, J. M., et al.	2009	USA	Cohort	51 patients	NPWT/RCOF and topical advanced moist healing strategies (non-NPWT)	
Dorafshar, A. H., et al.	2012	USA	RCT	87 patients	Patients with acute wounds treated with sealed gauze dressing and VAC	

	Direct costs	Indirect costs	Intangible costs	Results
	Hospital admissions and length of stay, number of surgical procedures and dressing changes, number of outpatient treatment visits, antibiotic usage, overall costs.	N/A	N/A	Compared to standard moist wound therapy (MWT), NPWT shows to be cost-effective measured in direct costs. The average total cost to achieve healing was \$25,954 for NPWT-patients, and \$38,806 for MWT-patients.
	Hospital length of stay, duration of treatment, medical costs	Infection, recurrence	Pain, irritability	Comparison between patients who were treated VAC therapy as first choice treatment (Gr. 1), and patients who were treated with various treatments before VAC or other treatments alone (Gr. 2). Gr. 1 demonstrated more rapid wound healing, early drainage control, shorter hospital stay, and mean hospital medical costs of €1,038 versus €2,137 for Gr. 2.
	Number of treatment-days, duration of treatment while in home care, length of stay	N/A	N/A	For each day NPWT was delayed, almost a day was added to the total length of stay.
	Median healing time, total cost per day, cost of labour time (time involvement of nursing staff), total costs	Bacterial load	Comfort	Comparison of VAC and other dressings. VAC represented higher comfort, less time involvement and costs of nursing staff, but overall costs were similar for both groups. As were time to primary endpoint (except for patients with diabetes and/or cardiovascular disease), wound surface reduction and bacterial clearance.
	Hospital length of stay, average wound volume reduction per day, total cost of care, cost per unit, cost per cubic centimetre reduction in volume, overall costs	N/A	N/A	Postsurgical LTAC patients who were treated by NPWT/ROCF had a more accelerated rate of wound closure, compared to patients treated with advanced moist wound-healing therapy. Lower cost per cubic centimetre volume reduction suggests that NPWT/ROCF produces a more favourable cost-effective solution.
	Wound surface area and volume, mean cost per day, time required for dressing change	N/A	Pain	GSUC is noninferior to VAC with respect to changes in wound volume and surface area in an acute care setting. In addition, GSUC dressings were easier and faster to apply, far less expensive (\$4.22/day vs. \$96.51/day for VAC) and less painful.

Dougherty, E. J.	2008	USA	Modelling study	N/A	Variuos treatments for full-thickness, nonhealing diabetic foot ulcers	
Driver, V. R. and P.A. Blume	2014	USA	Retrospective analysis of RCT study	324 patients	NPWT versus advanced moist wound therapy in treating diabetic foot	
Echebiri, N. C., et al.	2015	USA	Literature review + modelling study	N/A	Focus on NPWT vs. standard postoperative dressing in cesarean delivery	
Flack, S., et al.	2008	USA	Modelling study	N/A	Treatment of diabetic foot ulcers with VAC therapy or either traditional or advanced wound dressings	
Gabriel, A., et al.	2014	USA	Modelling study	82 patients	Patients with extremity or trunk wounds treated with standard NPWT (V.A.C. Therapy) or NPWTi-d (V.A.C. Veraflo Therapy)	
Ghatak, P.D.	2015	USA	RCT	30 patients	Treatment of chronic wounds with NPWT with and without use of a WED interface layer in the dressing	
Hampton, J.	2015	Denmark	Case-series	9 patients	Treatment of slow-healing leg- or pressure ulcers with NPWT	

Average 5-year direct wound care cost	N/A	QALYs	The average QALYs per modality were highest for treatment with PRP-gel (2.87), but next highest for NPWT-treatment (2.81). The lowest number of QALYs per modality was achieved with standard care and human fibroblast (both 2.65). The average 5-year direct wound cost was lowest for PRP-gel-treatment (\$15,159), next lowest for NPWT (\$20,964) and highest for standard care and human fibroblast (\$40,073 and \$40,569, respectively). Thus, PRP-gel represents a potentially attractive treatment, with NPWT as runner up.
Wound area reduction, total cost, median cost per 1 cm <sup>2</sup> of closure, cost of materials	N/A	N/A	Patients treated with NPWT experienced bigger wound area reduction (85%) than patients treated with AMWT (62%). The median cost per 1 cm <sup>2</sup> of wound closure was \$1,227 with NPWT and \$1,695 with AMWT; however, in the group of patients who achieved complete wound closure, the cost of NPWT excelled the cost of AMWT (\$10,172 vs. \$9,505).
Cost per treatment, cost of outpatient management	Cost of surgical site infection readmission	N/A	Among patients with a surgical site infection after caesarean delivery rate of 14% or less, standard postoperative dressing was the preferred cost-beneficial strategy. However, for patients with an infection rate greater than 14%, the use of prophylactic NPWT was preferred.
Cost per amputation avoided, cost per QALY, healing rate, overall cost of care	N/A	N/A	The model results demonstrate improved healing rates (61% versus 59%), more QALYs (0.54 versus 0.53) and an overall lower cost of care (\$52,830 versus \$61,757 per person) for patients treated with VAC therapy compared to advanced dressings.
Hospital length of stay, length of treatment, daily cost of therapy	Surgical debridements	N/A	The study showed a reduction in hospital length of stay, surgical debridements and LOT using NPWTi-d (V.A.C.Veraflo Therapy) compared to standard NPWT (V.A.C. Therapy). The comparative cost-effectiveness should be further assessed.
Number of dressing changes, cost per patients	Infection	Pain	Use of WED in conjunction with NPWT decreases the need for dressing changes from thrice to twice a week, and lowers the cost per patient from \$2952 to \$2345.
Healing rate, frequency of dressing changes, weekly cost of treatment	N/A	N/A	When introduced in the treatment of hard-to-heal wounds, 2 weeks of NPWT treatment helped achieve a reduced wound 10 weeks earlier than predicted, and healing rate continued after NPWT stopped. Frequency of dressing changes fell from 4 times weekly under conventional therapy, to 2 times a week with NPWT. Weekly cost of NPWT was on average 1.6 times higher than the baseline, but fell to 3 times less when NPWT stopped, owing to the reduction in dressing changes. NPWT is therefore concluded to be a cost-effective treatment for hard-to-heal wounds.

Hermans, M. H. E., et al.	2015	USA	Cohort	42 patients	Treatment of large wounds with either NPWT or hydrokinetic fibre dressing	
Hiskett, G.	2010	United Kingdom	Case-series	20 patients	Treatment of a variety of acute and chronic wounds with TNP in either hospital or home care settings	
Hop M. J., et al.	2014	The Netherlands	RCT	86 patients	Treatment of burn wounds with SSG with or without dermal substitutes (DS), and with or without TNP.	
Hutton, D. W. and P. Sheehan	2011	USA	Modelling study	N/A	Modern dressings, powered negative pressure and SNaP Wound Care System	
Inhoff, O., et al.	2010	Germany	Cohort	52 patients	Allogenic fascia lata, artificial skin substitute or NPWT for soft tissue reconstruction	
Kakagia, D., et al.	2014	Greece	RCT	50 patients with 82 leg fasciotomy wounds	Treatment of leg fasciotomies with either VAC or the shoelace technique	
Kaplan, M., et al.	2009	USA	Cohort	1058 patients	Early versus late initiation of NPWT in treating trauma wounds	



Reduction of wound size, total cost of materials, material cost per day and per wound, number of dressing changes	N/A	Pain	Healing trends were similar for wounds treated with hydrokinetic dressing and NPWT. Cost of materials were substantially higher for wounds treated with NPWT (\$2,301.55 per wound versus \$661.46 per wound for hydrokinetic dressings). Hydrokinetic dressings are therefore considered an effective substitute for NPWT.
Cost of direct wound treatment, cost per day, length of treatment	N/A	N/A	The cost of treating patients with TNP at home was less than the cost of treating patients at the hospital (£45.9 and £259.1 per day, respectively).
Costs of personnel, equipment, materials and housing, diagnostic costs, ICU costs, overall treatment cost, total cost, hospital length of stay,	Readmission days	Patient productivity loss, post-operative scar elasticity	Total costs were highest for patients treated with both DS and TNP due to high personnel, equipment and material costs (€2912). The second most expensive treatments were the treatment with DS (€2218), and the treatment with TNP (€2180). Thus, standard SSG treatment was by far the least expensive (€1703). 12 months post-operatively, scar elasticity was highest in scars treated with DS and TNP.
Average daily, monthly and bi-monthly costs, including material costs, clinic visit costs, hospitalisation costs, device rental and home health care payments. Long-term costs, including cost per patient with unhealed wound at end of 16 weeks. Fraction healed	Amputations, debridements, skin grafts, osteomyelitis	N/A	When compared to standard care, the SNaP system saves over \$9000 per wound treated and more than doubles the number of patients healed. The SNaP system has similar healing time to powered NPWT devices, but saves \$2300 in Medicare payments or \$2800 for private payers per wound treated. The SNaP system could thus save substantial treatment costs in addition to allowing patients greater freedom and mobility.
Length of stay, cost of hospitalization, material costs, duration of surgery, surgical costs, length of outpatient care, number of dressing changes	N/A	Postoperative healing rate, cosmetic results, scar stability	NPWT was the most expensive treatment due to high daily rental rates and frequent, time-consuming dressing changes (mean total cost: €7,521). Artificial skin substitute treatment was €4,557 in mean total cost, and the fascia lata group was least costly with a mean total cost of €4,475.
Wound closure time, mean daily cost	Infection, additional treatment with STSG	N/A	VAC requires longer time to definite wound closing than the shoelace method (19,1 days versus 15,1 days). Furthermore, VAC is far more expensive per day of treatment (€135 versus €14).
Number of hospital inpatient-and treatment days, length of ICU stay, ICU admission rate, total and variable costs per patient discharge	N/A	N/A	Early-group patients had fewer hospital inpatient days (10.6 versus 20.6 days), fewer treatment days (5.1 versus 6.0 days), shorter ICU stays (5.3 versus 12.4 days), and higher ICU admission rates (51.5 versus 44.5%) than the late group. Compared with late-group patients, early-group patients had lower total and variable costs per patient discharge (\$43,956 versus \$32,175 and \$22,891 vs \$15,805, respectively).

Karr, J. C., et al.	2013	USA	Case-control-series	20 patients	Various wounds treated with NPWT using a silver antimicrobial negative pressure dressing	
Lavery, L. A., et al.	2007	USA	Modelling study	NPWT group: 1135 patients, control group: 586 patients	Diabetic foot ulcer treated with NPWT or wet-to-moist therapy	
Law, A., et al.	2015	USA	Cohort	13,556 patients	Patients with chronic wounds treated with either VAC therapy from KCI or other non-KCI models of NPWT	
Lewis, L. S., et al.	2014	USA	Modelling study	N/A	Prophylactic NPWT compared to routine incision care following laparotomy for gynaecologic malignancy	
Mody, G. N., et al.	2008	India	RCT	48 patients	Comparison of locally constructed TNP devices to wet-to-dry gauze dressings in treating various wounds	
Monsen, C., et al.	2015	Sweden	RCT	16 patients	NPWT vs. alginate wound dressings in patients with deep peri-vascular groin infection	

Days to wound closure, wound treatment cost per patient, nursing time per patient	N/A	N/A	Patients treated with NPWT including a silver antimicrobial dressing experienced fewer days to wound closure than patients treated with standard NPWT (50.5 and 61.7 days, respectively). They also needed fewer hours of nursing time per patient (4.3 versus 15.4) and represented a significantly lower total cost per patient (\$826 versus \$5,181).
Successful treatment endpoint within timeframe, expected costs of therapy*	N/A	N/A	A greater proportion of the NPWT-group achieved successful treatment endpoint compared with wet-to-moist therapy at both 12 weeks (39.5% versus 23.9%) and 20 weeks (46.3% versus 32.8%). Expected treatment costs were alike for the two groups if one nursing visit per day for wet-to-moist patients is assumed, but 42% less for NPWT if two nursing visits per day are made. Thus, NPWT might decrease resource use by a given health-care system compared with standard wet-to-moist therapy.
Inpatient, emergency room and home and total costs, wound-related readmission rates*	Comorbidity scores	N/A	Patients treated with VAC therapy from KCI had lower mean total costs (\$80,768 versus \$111,212 measured 12 months after initial NPWT claim), lower wound-related costs (\$20,801 versus \$28,647 measured 12 months after initial NPWT claim) and lower hospital readmission rates than patients treated with other, non-KCI types of NPWT.
Reduction of cost of complication (being the target of the treatment), cost of treatment, reduction of cost of re-hospitalization*	N/A	N/A	The overall cost of incision are was \$104 lower for NPWT than for RF. At the lowest cost of NPWT (\$200), the risk of wound complication must be reduced by 33% for NPWT to achieve cost savings.
Material costs per dressing, total material cost for reaching satisfactory closure, duration of treatment	Complications	Pain	The material costs of one TNP dressing change (\$2.27) was app. 5.7 times more expensive than the materials used for one conventional dressing change (\$0.40). Total material costs for reaching satisfactory closure of two representative pressure ulcers were \$11.35 for TNP treatment and \$22 for conventional treatment. A review of the literature suggests that outcomes obtained using a locally constructed TNP device are similar to those obtained using commercially available devices.
Healing time, number of dressing changes, frequency of dressing changes outside hospital, personnel time, total hospitalised care cost, cost for wound material, personnel and polyclinical care	N/A	QoL (measured by mobility, self-care, usual activities, discomfort and anxiety/depression), pain	NPWT therapy in patients with deep peri-vascular groin infection can be regarded as the dominant strategy compared to alginate wound dressings, due to improved clinical outcome (median 57 and 104 days healing time, respectively), with equal cost and QoL-measurements.

Ozturk, E., et al.	2009	Turkey	Cohort	10 patients	Patients with Fournier's gangrene was treated with conventional therapy or VAC
Petkar, K. S., et al.	2011	India	RCT	40 split-skin grafts on 30 patients	Consecutive burn patients undergoing split-skin grafting received either conventional dressing or NPD
Rahmanian-Schwarz, A., et al.	2011	Germany	RCT	42 patients	Treatment of acute or chronic wounds with either VAC (KCI) or an alternative polyurethane foam-based NPWT system (RENASYS GO)
Rossi, P.G., et al.	2012	Italy	Literature review	17 articles reporting cost analyses	NPD versus conventional treatments in treating various wounds
Sakellariou, V. I., et al.	2011	Greece	Cohort	32 patients	Patients treated for bone and soft-tissue sarcomas and secondary wound-healing complications with NPWT or conventional treatment
Tuffaha, H. W., et al.	2015	Australia	Modelling study including RCT pilot study	92 patients in pilot trial	NPWT for reducing SSI for obese women undergoing caesarean delivery
Vaidhya, N., et al.	2013	India	RCT	60 patients	Treatment of diabetic foot wounds with either NPWT or conventional treatment
Vuerstaek, J. D. D., et al.	2006	The Netherlands and Belgium	RCT	60 patients	Treatment of chronic leg ulcers with VAC or conventional wound care techniques
Warner, M., et al.	2010	USA	Cohort	24 patients	VAC versus antibiotic bead pouch for the treatment of blast injury of the extremity

	Total cost, length of stay, healing success rate, number of dressing changes, hands-on treatment time	N/A	Pain, need for analgesics, mobility, eating habits, ability to shower, patient convenience, ease-of-use	VAC therapy is superior to conventional therapy in regards to patient QoL when treating Fournier's gangrene. Healing success rate and total costs were similar.
	Material costs, graft take (healing rate), duration of dressing	Treatment adverse events, re-grafting	Patient convenience	NPT improves graft take in burns patients and can be assembled using locally available materials. No conclusion on total costs.
	Median healing time, duration of treatment, number of dressings, total and daily material costs	Adverse events, skin reaction	N/A	Material costs were in average 11.7% lower for the polyurethane foam-based NPWT system than for VAC (KCI). There were no significant difference in healing rates.
	Various items included from study to study	N/A	N/A	Some clinical and economic benefit of NPT in severe chronic and acute wound treatment can be derived from the literature review.
	Length of stay, total costs, cost per day	Complications e.g. infections	N/A	Patients treated with NPWT had a significantly shorter length of stay than patients undergoing conventional treatment (mean of 16.5 days versus 25.2 days). Mean total cost for NPWT treatment was \$4,867.3, and \$11,680.1 for conventional treatment. Mean cost per day for NPWT treatment was \$295.1 and \$463.6 for conventional treatment.
	Total costs, effect and EVPI for adopting NPWT	N/A	N/A	The incremental net monetary benefit of NPWT was AUD 70, indicating that NPWT is cost-effective compared with standard dressings. The probability of NPWT being cost-effective was 65%.
	Number of dressings, length of treatment, success healing rate, cost per dressing, average total cost. In less detail: cost of daily treatment, hospital stay and morbidity.	Worsening of condition, requirements of antibiotics	Requirements of analgesics	End point of treatment was achieved in 17.2 days for NPWT group compared to 34.9 days for the control group, and overall success rate was larger in NPWT group than in control group (90% versus 76.6%). Number of dressings were 7.46 for NPWT group and 69.8 for control group, and with a cost per dressing of Rs. 500 and Rs. 200 respectively, average cost of NPWT was lower than conventional dressings (Rs. 3,750 versus Rs. 7000).
	Time to complete healing, time for wound bed preparation, total cost including costs for materials and personnel	Treatment adverse events, recurrence	QoL (measured by mobility, self-care, usual activities, discomfort and anxiety/depression), pain	VAC should be considered as the treatment of choice for chronic leg ulcers owing to its significant advantages in the time to complete healing (29 days versus 45 days for conventional methods), its shorter wound bed preparation time (7 days versus 17 days for conventional methods), and the 25–30% lower total costs.
	Total costs, including costs of materials and cost of surgical set-up/charge to surgery facility	Infections, returns to operating room, more surgeries	N/A	VAC therapy costs in average app. \$1000 more per patient than the antibiotic bed pouch in treating blast injuries in the extremities.

Webster, J., et al.	2014	Australia	Systematic literature review	9 studies	NPWT delivered by any mode compared to any standard dressing or any advanced dressing, or comparisons between different NPWT devices
Whitehead S. J., et al.	2011	France	Modelling study	N/A	VAC vs. advanced wound care for the treatment of diabetic foot ulcers
Yang, C. K., et al.	2015	US	Case-series + review of medical cost estimators	10 ulcers on 7 patients	Treatment of massive chronic venous leg ulcers with NPWT
Yao, M., et al.	2012	US	Cohort	342 patients	Patients with multiple significant comorbidities and chronic lower extremity ulcers treated with both early, intermediate and late NPWT, as well as standard care
Zameer, A., et al.	2015	India	RCT	60 patients	Comparison of custom made VAC therapy and conventional wound dressings in treating non-healing lower limb ulcers
Zhen-Yu, Z., et al.	2016	China	Cohort	76 patients	Prevention of SSI after ankle surgery using VAC on diabetic patients
* Reimbursement data included					

	Time to complete healing, costs including treatment costs, cost of health practitioner time or visits, cost of hospital stay	Treatment adverse events, mortality, re-operation, infections	Pain, QoL, life years gained, QALYs	There are clear cost benefits when non-commercial systems are used for NPWT, with no evidence of worsening of clinical outcome, and with lower pain level ratings for non-commercial systems.
	QALYs, healing rate, total cost of care	Amputation rate	N/A	Patients treated with VAC therapy experienced more QALYs (0.787 versus 0.784 for patients treated with AWC), improved healing rates (50.2% versus 48.5%) and a lower total cost of care (€24,881 versus €28,855).
	Length of stay, healing success rate after 6 months, estimated costs	N/A	N/A	NPWT (with STSG) treatment is more effective for closure of massive VLU at 6 months than that reported for standard compression therapy. Further, the cost of NPWT is comparable with standard compression therapy (estimated \$27,000 and \$28,000, respectively).
	Time for wound closure	N/A	N/A	Patients receiving NPWT were 2.63 times more likely to achieve wound closure than patients receiving standard care. Compared with late NPWT users, early and intermediate NPWT users were 3.38 and 2.18 times more likely to achieve wound healing, respectively.
	Wound size reduction, time to wound closure	N/A	Patient blood sugar stability (diabetes)	The custom made VAC system showed good results in healing rate. The study does not report on costs.
	Hospital length of stay, SSI rate, hospital costs	N/A	N/A	The incidence of SSI was significantly lower in the VAC group (4.6%) than in the SMWC group (27.8%). The hospital length of stay was also slightly lower, although not significantly (12.6 +/- 2.7 versus 15.2 +/- 3.5). The difference in hospital cost was also insignificant (6843.2 +/- 1195.3 versus 9456.2 +/- 1106.3).

### Appendix 13. Non-comparative studies

Author	Year	Country	Type of study	Study population	Intervention
Chaput, N., et al.	2015	France	Case-series	23 patients	Treatment of acute or chronic wounds with a specially designed inexpensive NPWT called PROVACUUM
Rozen, W. M., et al.	2007	Australia	Case-series	9 patients	Treatment of lower limb split-skin grafting with an alternative method of negative pressure dressing comprised by a single cut fom sheet, a conventional disposable closed-system suction drain and an adhesive dressing
Searle, R. and J. Milne	2010	UK	Narrative review	N/A	NPWT in general
Shalom, A., et al.	2008	Israel	Case-series	15 patients	Treating complex wounds with a homemade NPWT system
Trueman, P.	2008	US	Literature review	N/A	VAC therapy in home health settings
Verhaalen, A., et al.	2010	US	Case-series	8 patients	Wounds with enteroatmospheric fistulae, treated with NPWT supplemented by a impermeable tubular structure isolating the fistula



	Direct costs	Indirect costs	Intangible costs	Results
	Number of dressing changes, length of treatment, average treatment cost	Complications	Ease of use, pain	Surgeons found that the low-cost alternative NPWT device was similar to commercial NPWT devices.
	Treatment cost, rate of skin graft take, length of inpatient stay	Complications	Patient toleration	The cost of five days of treatment with the alternative method of negative pressure dressing (\$577) was significantly lower than the expected cost of five days of treatment with commercial VAC dressing (\$2603).
	Material costs, cost of nursing time, resources used per dressing change	N/A	N/A	Evidence suggests that although the unit cost of NPWT may be perceived to be high, there is a real possibility that materials and rental costs can be offset by, for example, reduction in length of stay, lower frequency of dressing change, and a reduction in complications and further surgical interventions. Further cost-effectiveness studies are essential.
	Cost per day, material costs	Complications	N/A	The homemade NPWT system obtained results similar to that could be expected with the VAC (KCI) system in all parameters. Cost per day using the homemade system for a 10cm <sup>2</sup> wound is about \$1, compared with \$22 using the VAC (KCI) system.
	Hospitalisation rate, total cost per healed wound	N/A	N/A	One of the reviewed studies showed that patients treated with NPWT in home care settings had significantly less hospitalisations. The overall conclusion is, that the use of NPWT outside hospital settings has the potential to improve the efficacy of wound management and help reduce the reliance on hospital-based care, which in turn can reduce the overall cost.
	Material costs, hospital dischargement rate	N/A	N/A	The technology was successful in isolating the fistula. Successful isolation of fistulas when using NPWT has the potential to lower health care costs by allowing for earlier hospital discharge.

## Appendix I4. Flowchart - health economic studies

