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## CASE REPORTS

# Negative pressure wound therapy versus healing by secondary intention in pressure ulcers

Roberto Cirocchi, Georgi Popivanov, Ventsislav M Mutafchiyski, Andrea Boccolini, Justus Randolph, Massimo Lancia, Luigi Carlini, Tomasz Banasiewicz

REVIEW

***Abstract*—: Pressure ulcers are a highly prevalent source of morbidity with an equally high incidence of up to 38.0% amongst different categories of healthcare institutions. Therefore, the management and therapeutic approach toward these often hospital- or facility-acquired problems remain critical aspects of long-term care. Negative pressure wound therapy (NPWT) has proven effective in addressing the barriers to pressure ulcer healing including increasing blood flow to previously ischemic wound areas by generating subatmospheric pressure which vacuums in circulation. The objective of this study was to compare negative pressure wound therapy (NPWT) versus surgical wounds healing by secondary intention (SWHSI). A systematic literature search was conducted using the PubMed and Scopus search engine up until the 20 Th January 2017 including the terms: "negative pressure wound therapy" and "pressure ulcers". In this systematic review, six randomized controlled trials were included. NPWT is deemed appropriate and effective method and widely used by clinicians to promote the healing of wounds and ulcers of different etiology. The heterogeneity found in individual trials regarding the inclusion criteria, therapeutic procedures, the criteria and methods of outcome evaluation, however, did not allow for a data evaluation with statistically valid conclusions. It is reasonable to assume that a subset of patients with pressure ulcers can be effectively treated with NPWT, with optimal results and good cost-benefit ratio, also with respect to the quality of life.**

***Keywords*—NPWT, VAC, Negative pressure wound therapy**

## I. Introduction

PRESSURE ulcers are a significant source of morbidity with an equally high incidence of up to 38.0% amongst different categories of healthcare institutions.[1, 2] In particular this condition affects people aged over 65 years with a prevalence ranging from 0.3% to 46% and an incidence ranging from 0.8% to 34%.[3] Therefore, the management and therapeutic approach toward these often hospital- or facility-acquired problems remain critical aspects of long-term care.[4] Often, complexities exist structurally within these wounds including undermining, tunneling, and sinus tract formation along with exudate and necrotic tissue.[5] These serve as barriers to healing as they may host resident and occult sources of foreign bodies as well as unreachable nonviable material, both of which may promote ischemia, inflammatory responses, and an increased susceptibility to pathogenic invasion.[6–10] Pressure ulcers and their complications, such as infection and sepsis, especially when hospital-acquired, can raise medico-legal issues. Therefore, an accurate planning of the best therapeutic options for the patient is essential. Negative pressure wound therapy (NPWT) has proven effective in addressing the barriers to pressure ulcer healing including increasing blood flow to previously ischemic wound areas by generating subatmospheric pressure.[6] By suctioning the pro-inflammatory cytokines and enzymes are furthermore decreased,[7, 8] while favorable healing factors such as the infiltration of vascular endothelial growth factor (VEGF) and chemotaxis of fibroblasts increase angiogenesis.[9, 10] Due to the mechanical washout of the wound bed, the pathogenic load is decreased thus indirectly lowering the toxic burden on the pressure wound.[6]

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## II. Methods

### A. Objectives

The objective of this study was to compare negative pressure wound therapy (NPWT) versus surgical wounds healing by secondary intention (SWHSI).

### B. Types of studies

Randomized controlled trials (RCTs) were identified through a systematic review of published literature (full article, thesis, or abstract).

### C. Types of participants

Patients presenting with pressure ulcers in any location.

### D. Types of interventions

The types of interventions were NPWT in experimental group versus SWHSI in control group (surgical debridement, enzyme or chemical necrosectomy) Types of outcome measures The primary outcomes of interest were summarized

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in efficacy (healed of ulcer, reduction of ulcer volume, local improvement in ulcer characteristics), the secondary outcomes in the socio-economic advantages (consumption of health resources).

### *E. Studies selection*

A systematic literature search in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standards,[11] was conducted using the PubMed and Scopus search engine up until the 20 Th January 2017 including the terms: "negative pressure wound therapy" and "pressure ulcers". No language, publication date, restrictions were imposed. All titles and abstracts of the considered studies were analysed to select only the studies that reported the PICO (P = Patient, Population or Problem; I = Intervention; C = Comparison; O = Outcome).[12] When multiple articles were published from a single study group and overlapping study periods were reported, only the most recent article was considered so as to avoid duplication of data. The Pubmed function "related articles" was used to enlarge each search, and the reference list of all potentially eligible studies was analysed. To minimize retrieval bias, a manual search method including the Science Citation Index Expanded, Scopus and Google Scholar databases was performed. After this initial process, the full-text papers were independently screened by 2 authors for eligibility. The final decision on eligibility was reached by consensus between the 2 screening authors. Data were extracted by 2 authors based on an intention-to-treat principle. Any disagreement was resolved through discussion with a reassessment of the data and/or by involving a third author. The methodological quality assessment of the included studies was evaluated with the instructions and the items given in the Cochrane Handbook for Systematic Reviews of Interventions (sequence generation and allocation concealment for selection bias, blinding of participants or personnel for performance bias, blinding of outcome assessors for detection bias, incomplete outcome data for attrition bias and selective reporting bias)[13–16] A protocol for this meta-analysis has been registered on PROSPERO database (ID: CRD42017059678).

## III. RESULTS

The PRISMA flow diagram for systematic reviews is presented in (Fig. 1). We identified 76 publications using the literature search strategy described above. After excluding 63 records following the review of the titles and abstracts, 13 abstracts eligible for full-text evaluation remained. After full-text assessment, we excluded 7 studied[17–23] (Tab. I) and identified 6 publications that fulfilled the inclusion criteria which reported data about pressure ulcers (Tab. II).[24–29] Quality assessment of the included studies. Since all the included studies are RCTs the quality assessment was based on the risk of bias. Overall risk of bias of the included studies was low as reported in table 3.(Tab. III) In the pressure ulcers analysis, the stage of ulcers was reported in all trials and it was the same (III and IV stage). In three studies the authors described the etiology of immobilization and reported a traumatic paraplegia. The location of ulcer was reported in five studies and it was exclusively sacral in the paper of Dwivedi[24] and Wild,[27] differently Ashby[25] and Ford[29] reported a mix of locations: sacral, ischial, lateral malleolar and trochanter region. Overall, 141 patients were enrolled: 62 underwent NPWT and 79 other conventional treatments. All the included trials reported different types of outcomes, so the reported outcomes were not comparable. The analyzed outcomes are extremely numerous and are categorized in some different groups: ulcer healing, reduction of ulcer volume, local improvement in ulcer characteristics and consumption of health resources. Only two trials evaluated ulcer healing: Ashby[25] and de Laat.[26] In the first study only one pressure ulcer (16.6%) which underwent NPWT (79 days) healed; in the other study the authors performed a subgroup analysis of patients with pressure ulcers, but they did not describe the results and reported only the conclusion ("statistically significantly faster wound healing in the topical negative pressure group")[20] (Tab. IV).

Three trials described the reduction in ulcer volume, but the outcome descriptions were very inconsistent [24,28,29]. Dwivedi reported the length and width of ulcer,[24] differently Wanner reported the mean (SD) time to reach 50% of the initial volume[28] and Ford reported the mean percent reduction in ulcer volume.[29] In the first study the length and width of an ulcer decreased significantly ($p<0.01$) in NPWT group compared to standard care group at week 9.[24] In the other two studies the authors did not report a significant difference between the two groups, respectively in Wanner 27 days in NPWT group and 28 in the traditional treatment and 51.8% with NPWT in Ford and 42.1% with traditional treatment[28, 29] (Tab. IV) . The authors' choice of the characteristics for the local evaluation of ulcer improvement was very heterogeneous. These characteristics were macroscopically evaluated through a biopsy with a histologically examination. In the macroscopic examination, the presence of the granulation tissue was the most important favorable prognostic sign. The evaluation of this tissue was performed in different modalities: newly-formed granulation tissue and wound contracture (measured the volume instead of the area of the usually undermined wounds) as reported from Wanner [28], the absolute and relative proportion of wound surface granulation tissue as reported from Wild[27] or the conversion of slough into red granulation tissue as reported from Dwivedi.[24] Conversely the presence of exudates, fibrin or necrosis were poor prognostic signs: absolute and relative proportion of fibrin tissue at the wound base or absolute and relative proportion of necrosis. Only few significantly better results were reported in patients who underwent NPWT (lower exudates in NPWT group at weeks 4 and 9 and higher conversion of slough into red granulation tissue, increase in surface granulation), differently the other evaluation did not report report any advantage in macroscopic (newly-formed granulation tissue and wound contracture, absolute and relative proportion of fibrin tissue at the wound base and of necrosis) or biopsy evaluation (mean number of PMNs and lymphocytes per high-power field and mean number of capillaries per high-power field). (Tab. IV) The analysis of

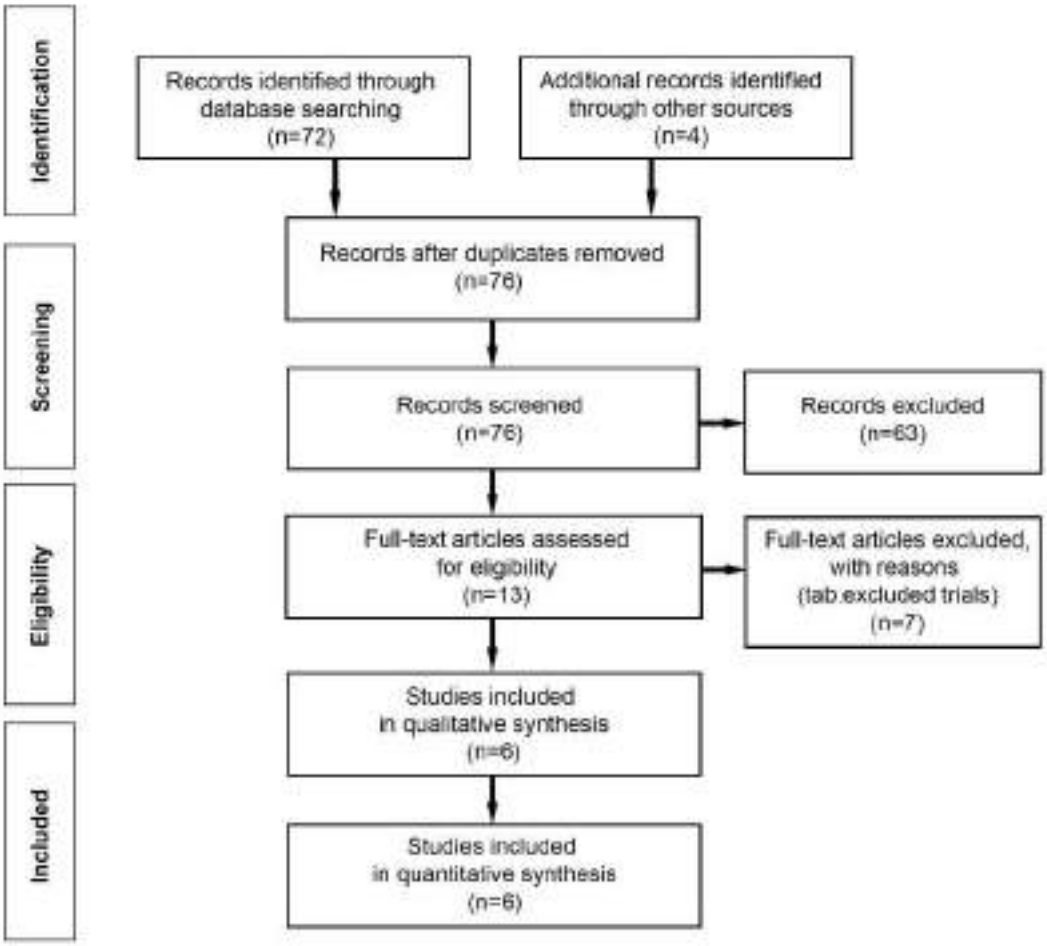


Figure 1. PRISMA flow diagram of the analyzed papers

costs was evaluated only from Wanner, that did not report any data but only the conclusion about NPWT "cheaper than the traditional dressings",[28] other studies reported the indirect costs as the discharge from hospital, the mean number of treatment visits per week or the median number of dressing changes per day. Dwivedi reported that the hospital stay was significantly lower (p=0.001) in NPWT at week 2.[24] Ashby reported a lower mean number of treatment visits per week in patients who underwent NPWT (3 vs 6),[25] whereas Wild reported only that lower dressing changes resulted in patients who underwent NPWT[27] (Tab. IV). The quality of life was evaluated only from Wanner and it was better in patients underwent NPWT, but without reporting of any data.[28] In the surgical wounds healing by secondary intention (SWHSI) all the studies described the type of procedure performed and the locations of the incision.

## IV. Discussion

The wound healing is a complex regenerative process with multifactorial determination. Despite the recent advance in medicine the patients with various pressure ulcers still represent a major concern due to lack of an effective treatment. Moreover, in the light of the modern laparoscopic surgery and a strive to diminish hospital costs these patients are not "desirable" because of the significant burden on the nursing staff, prolonged hospital stay, expensive treatment and unsatisfactory results. The total cost in United Kingdom is between 1.4 and 2.1 billion annually,[4] which is confirmed by a recent systematic review.[30] Unfortunately, despite the intensive research in this particular area, there are few RCTs in the literature yet. The evidence-based analysis of Medical Advisory Secretariat of Ontario Ministry of Health and Long-Term Care published in 2009 concluded that "the role of NPWT in chronic pressure ulcers remains unclear".[31] A Cochrane based systematic review of RCTs of Dumville et al. published in 2015, reported „no rigorous RCT evidence available regarding the effects of NPWT compared with alternatives for the treatment of pressure ulcers. High uncertainty remains about the potential benefits or harms, or both, of using this treatment for pressure ulcer management".[32] In this systematic review, six randomized controlled trials were included.[24–29] In the two groups the characteristics of patients were similar, but the high heterogeneity regarding interventions, comparisons and outcomes rendered the data

Table I
EXCLUDED STUDIES

| Author, year of publication | Reasons of exclusion |
|---|---|
| de Laat 2017 | A cross-sectional survey self-management of pressure ulcer prevention in adult paraplegics. |
| Skrinjar 2016 | In this randomized controlled trial the Authors analyzed , 60 consecutive patients with chronic leg wounds or surgical site infections after revascularization of lower extremities and compared of Negative Pressure Wound Therapy additional polymeric membrane interface dressing (PMD; PolyMem WIC) versus Negative Pressure Wound Therapy alone |
| Sáez-Martín 2015 | In this randomized controlled trial the Authors analyzed ten patients with nonhealing ulcers and compared a novel biocompatible polyurethane foam versus the conventional foam |
| Wagstaff 2014 | In this randomized controlled trial the Authors analyzed twenty pressure ulcers and compared negative pressure and nanocrystalline silver dressings versus negative pressure wound therapy alone |
| Tuncel 2013 | In this randomized controlled trial the Authors analyzed 50 consecutive patients with wound and compared conventional antiseptic (polyhexanide solution) dressings, versus saline-soaked antibacterial gauze-based negative pressure wound therapy |
| Dunn 2011 | This prospective multi-center non-comparative study reported the use of gauze-based Negative Pressure Wound Therapy in 131 patients with in chronic and acute wounds |
| Kordestani 2008 | In this randomized controlled trial the Authors analyzed eighty-five patients with diabetic foot ulcers, pressure ulcers or leg ulcers and compared bioactive study dressing versus control dressing alone |

Table II
CHARACTERISTICS OF THE INCLUDED STUDIES

| | Type of study | Nation were perfomed the trial | Etiology of immobilization | Location of ulcers and stage | Patients underwent NPWT | Patients underwent conventional treatment |
|---|---|---|---|---|---|---|
| Dwivedi 2016 | RCT | India | Traumatic paraplegia | Sacral / III and IV stage | 21 | 23 |
| Ashby 2012 | RCT | UK | NR | Heel, Trochanter, Sacrum, Gluteal, Ischial / III and IV stage | 6 | 6 |
| De Laat 2011 | RCT | The Netherlands | Traumatic paraplegia | NR / IV stage | 6 | 6 |
| Wild 2008 | RCT | Austria | NR | Sacral / III and IV stage | 5 | 5 |
| Wanner 2003 | RCT | Switzerland | Traumatic paraplegia | Sacral / III and IV stage | 11 | 11 |
| Ford 2002 | RCT | USA | NR | Ischial, Sacral, Lateral malleolar, Trochanter and Calcaneal / IV stage | 20 | 21 |

not suitable to perform meta-analysis. All trials have agreed that the pressure ulcers healed better in patients underwent NPWT, but the data reported are very poor. Ashby showed that only one pressure ulcer (17%) healed in NPWT group,[25] whereas de Laat reported only a "statistically significantly faster wound healing".[26] Different results were found in the trials that described the reduction in ulcer volume with different type of measure – length and width of ulcer, mean (SD) time to reach 50% of the initial volume, mean percent reduction in ulcer volume). In this outcome the results are different: Dwivedi reported statistically significant better results in patients underwent NPWT.[24] In contrast, Wanner[28] and Ford[29] did not find a significant difference between the two groups. A small retrospective case series of 20 patients with various wounds (2 pressure ulcers) reported mean reduction of wound area with 29% after treatment with V.A.C.® (KCI).[33] The authors reported reduction of the pressure ulcers size with 52 and 13 mm after 26 and 32 days with NPWT, respectively. In a RCT (79% pressure ulcers) Joseph et al. reported volume reduction in 78% in NPWT vs. 30% in the conventional group and 64% granulation tissue proven histologically after 6-weeks treatment.[34] Despite the low evidence level several case reports showed reduction of wound volume and complete healing in two months.[35, 36] The same problem was encountered in the analysis of very heterogeneous characteristics for the local evaluation of ulcer improvement. One study showed only few significantly better results in patients underwent NPWT (lower exudates in NPWT group at weeks 4 and 9, higher conversion of slough into red granulation tissue and an increase of the surface granulation).[24] Differently, the other evaluations reported no advantage in macroscopic (newly-formed granulation tissue and wound contracture, absolute and relative proportion of fibrin tissue at the wound base and of necrosis)[27, 28] and biopsy evaluation (mean number of PMNs and lymphocytes per high-power field and mean number of capillaries per high-power field).[29] In the most recent work from China the authors compare conventional treatment with NPWT

Table III
RISK OF BIAS. (YES E.G. LOW RISK OF BIAS; NO E.G. HIGH RISK OF BIAS)

| | Selection bias | Performance bias | Attrition bias | Detection bias | Reporting bias |
|---|---|---|---|---|---|
| Dwivedi 2016 | Yes | Yes | Unknown | Unknown | Yes |
| Ashby 2012 | Yes | Yes | Yes | Yes | Yes |
| De Laat 2011 | Yes | Yes | Unknown | No | Yes |
| Wild 2008 | Yes | Yes | Unknown | Unknown | unknown |
| Wanner 2003 | Unknown | Unknown | Unknown | Unknown | Yes |
| Ford 2002 | Yes | Yes | Unknown | Yes | Yes |

Table IV
COMPARISON OF THE THERAPY OUTCOMES AFTER THE INTRODUCTION OF NPWT

| | Lesion reduction | Outcomes |
|---|---|---|
| Ashby 2012 | Only one pressure ulcer healed (NPWT group) during follow-up (time to healing 79 days). | mean number of treatment visits per week: 3.1 (NPWT) and 5.7 (SC); 6/6 NPWT and 1/6 SC participants withdrew from their allocated trial treatment. |
| De Laat 2011 | statistically significantly faster wound healing in the topical negative pressure group | |
| Dwivedi 2016 | Significantly (p<0.01) decreased in NPWT group as compared with standard care group at week 9. At weeks 1, 2 and 3, depth was significantly (p<0.05) higher in NPWT group, whereas at week 9 a significant reduction (p=0.01) was observed | Secretion: Significantly (p=0.001) lower in NPWT group at weeks 4 and 9; Conversion of slough into red granulation tissue: Significantly higher in NPWT group (p=0.001<br>Discharge from hospital (p=0.001) lower in NPWT at week 2 |
| Wanner 2003 | 27 (10) days in the vacuum-assisted group and 28 (7) in the traditional group | Newly-formed granulation tissue and wound contracture (measured the volume instead of the area of the usually undermined wounds) equally effective<br>NPWT cheaper than traditional dressings, QoL improved more |
| Ford 2002 | $42.1\%$ with HP and $51.8\%$ with VAC ($p = 0.46$) | Mean number of PMNs and lymphocytes per high-power field: Decreased in the VAC group and increased in the HP group<br>Mean number of capillaries per high-power field: The mean number of capillaries per high-power field was greater in the VAC group<br>Improved biopsy-proven osteomyelitis underlying the ulcers: Improved with VAC |
| Wild | Increase in fibrin tissue at the wound base of 21.8%, whereas in the V.A.C group, a 27% reduction was observed ($P0.035$)<br>Necrosis insignificantly reduced in the V.A.C. group | Increase in surface granulation tissue of 54% was observed in the V.A.C. group and a reduction in the Redon group ($P0.001$). |

and NPWT plus microplasma using the following outcome measures – the maturity of granulations, growth degree of epithelium, blood perfusion, density of new vessels, wound area and total healing rate.[37] The combination of NPWT with microplasma yielded the best results followed by NPWT alone and conventional treatment. The quality of life (QoL) was evaluated in only one trial.[38] The authors reported a better quality in NPWT group, but without any data. Similarly, in various acute or chronic wounds, others reported better QoL.[30, 39] In fact, a true cost analysis was not performed. Wanner,[28] wrote only that NPWT was "cheaper than the traditional dressings". In the other studies, reporting indirect costs (discharge from hospital, the mean number of treatment visits per week or the median number of dressing changes per day), the authors showed better results in NPWT group.[24, 25] In 2004 the German and Austrian Societies for Wound Healing and Wound Management stated that NPWT treatment is cost effective.[38] In a RCT with 65 cases Braakenburg et al. reported similar overall costs.[40] In 2008, Apelqvist et al. reported significantly lower costs in NPWT group vs. standard moist wound therapy of diabetic foot wounds (with average 12 852 $).[41] A systematic review of National Health Service of UK supported the usage of NPWT in chronic wound management due to better QoL and improved cost effectiveness.[39] The work encourages development of national guideline for NPWT in wound management.

## V. CONCLUSION

NPWT is deemed appropriate and effective method and widely used by clinicians to promote the healing of wounds and ulcers of various etiology. High quality clinical studies are nevertheless few and do not allow to draw definitive conclusions. The analysis of the selected trials showed an overall favorable trend for NPWT compared to conventional therapy, in particular in a wounds with low secretion and presence of granulation tissue. This would seem to indicate that the NPWT should not be used too early in pressure ulcers. The heterogeneity found in individual trials regarding the inclusion criteria, therapeutic procedures, the criteria and methods of outcome evaluation, however, did not allow for a data evaluation with statistically valid conclusions. The outcome heterogeneity between studies suggests that NPWT cannot be indiscriminately considered the standard treatment for pressure ulcers. An adequate and detailed information should be provided, in order to acquire a valid patient's consent to NPWT. In fact, considering the lack of an effective treatment of pressure ulcers, the patient should be given an appropriate range of choices, in order to express his consent to undergo the best therapeutic option for the specific case. It is reasonable to assume that a subset of patients with pressure

ulcers can be effectively treated with NPWT, with optimal results and good cost-benefit ratio, also with respect to the quality of life[41, 42] Further clinical studies are needed on homogeneous groups of patients with homogeneous inclusion criteria, therapeutic procedures and outcome measures. In our opinion, it is mandatory to include patients with uniform characteristics in the new Randomised Controlled Trials' design: age, nutritional status, comorbidities, stage and size of pressure ulcers. Furthermore, we suggest to report the following principal outcomes: treatments failure rate, complete healing time, quality of life during treatment and wound care cost.

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# Management of an open abdomen complicated by a high output entero-atmosferic fistula after a gastric by-pass

Lorena Hierro-Olabarria Salgado

CASE REPORT

***Abstract*—: There is a wide spectrum of indications for negative pressure wound therapy (NPWT) including enterocutaneous fistulas, open abdomen management, abdominal wound dehiscence, open fractures, amputation wounds, sternal wound infections, vascular bypass site infection and many others. The article shows a case report of a patient with an entero-atmospheric fistula managed with NPWT. Control of intestinal contents from an entero-atmospheric fistula with the NPWT minimizes the damage to the healing bed of granulation tissue until the definitive closure of the fistula can be undertaken six to twelve months later.**

**After a laparoscopic gastric bypass and 5 emergency interventions because of leaks at the jejunojenunal anastomosis and complications of the abdominal wall, an entero-atmospheric fistula appeared. This fistula was managed with the NPWT during two months. In the described case, the application of negative pressure dressing system allowed the management of the entero-atmospheric fistula until it became a stoma.**

***Keywords*—gastric bypass, jejunojejunal anastomosis leak, abdominal wall closure, laparostoma, enteroatmospheric fistula, NPWT**

## I. Introduction

ENTERO-ATMOSFERIC fistulas occur in the midst of an open abdomen with no overlying soft tissue. These are one of the most difficult complications of "damage control" laparotomy and are a source of significant morbidity and mortality.[1] The main goal in managing external fistulas is to control the enteric contents at the source of the fistula to protect the skin from corrosive effects of the enteric or pancreatic fluids contents, and to facilitate nursing care of the patient.[2, 3] Control of intestinal contents from an entero-atmospheric fistula will minimize damage to the healing bed of granulation tissue until the definitive closure of the fistula can be undertaken six to twelve months later. It may require surgical diversion to convert the gastrointestinal opening into a stoma that can thus be controlled. NPWT can also simplify management of entero-atmospheric fistula. The continuous suction of the fistula output minimizes contact time between the intestinal fluid and the exposed peritoneum, allowing effective control of intestinal spillage. Care must be taken when applying a negative pressure wound dressing in the setting of exposed (but uninvolved) bowel since it can cause formation of additional fistulas, especially if fresh suture or staple lines in the bowel are exposed.[4] Additional protection can be provided by placing another layer of plastic or a biologic dressing between the bowel and the negative pressure sponge.[5] In this paper, we present a complex case of an entero-atmospheric fistula, highlighting the importance of the NPWT and the different dressing options in this therapy.

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## II. Case Report

A 67- year-old woman was operated on in our hospital on April 2016 for morbid obesity by the Esophagogastric surgical team; a programmed laparoscopic bypass was performed. The 8th day after surgery she presented with clinical and analytical worsening, compatible with intestinal obstruction. (Fig. 1) Computed tomography (CT) with contrast-media enhancement images revealed a dilation of the alimentary limb and a wrinkle or obstruction at the Roux-en-Y connection. Emergency surgery was immediately performed with a laparotomic approach. The findings were a wrinkle of the jejuno-jejunal anastomosis that was causing an obstruction and dilation of the alimentary limb. During manipulation, the alimentary limb was perforated. A section of the distal portion of the bilio-pancreatic limb and a new end to side anastomosis was performed. The perforation of the alimentary limb was treated with simple suture.

Five days after the patient underwent a new emergency surgery. This time the complication was a leak of both extremes of the Roux-en-Y (or jejuno-jejunal) anastomosis and also of the suture of the alimentary limb. The surgical team carried out a section of the alimentary limb from the stitches that had failed to the Roux-en-Y (distal) and a new end to end manual anastomosis leaving a 100 cm long remnant alimentary limb. Finally, they performed a new side to side anastomosis for the jejuno-jejunostomy, distal from the previous anastomosis (Fig. 2). The abdominal wall closure was difficult because it was under tension, so they

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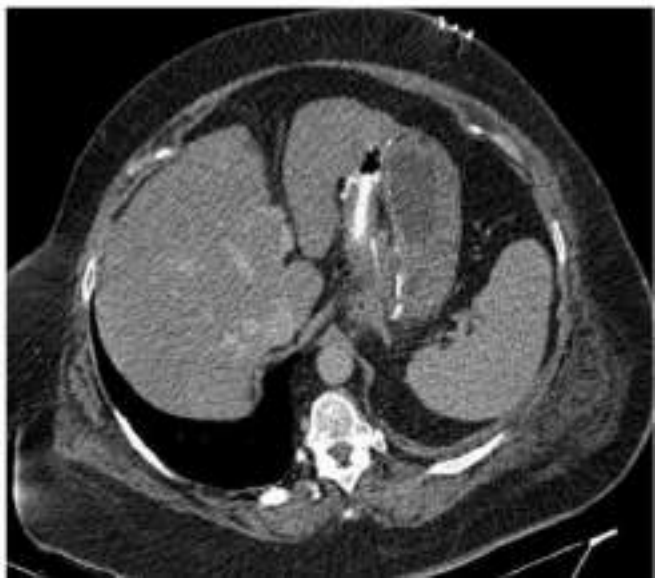

Figure 1. Computer tomography (CT) with contrast—media revealed a dilation of the alimentary limb and a wrinkle or obstruction at the Roux-en-Y connection.

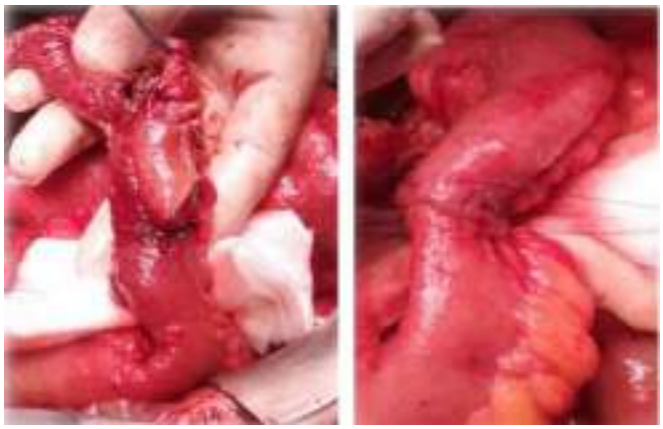

Figure 2. Leak of both extremes of the jejuno-jejunal anastomis. End to end manual anastomosis

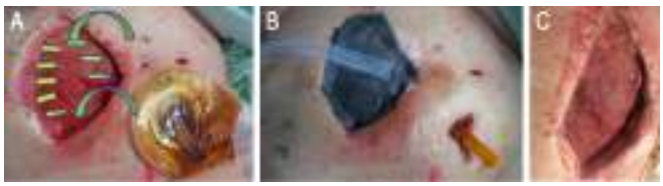


Figure 3. A: Laparostoma in midline and drainage with a stoma bag on jejunojunestomy leak. B: Placement of the NPWT dressing, C: Wound appearance after NPWT

Figure 4. Entero-atmospheric fistula with the feeding catheter at the distal loop.

decided to make a lateral incisions of both anterior rectus abdominis sheaths and then close the wall with Smead-Jones Polydioxanone stitches.

The abdominal closure was complicated six days later because of a subcutaneous haematoma with an active bleeding. The patient again underwent surgical treatment with another laparotomy, where a partial leak of the jejuno-jejunostomy was identified and treated with some simple stitches. Closure of the abdominal wall again was carried out, this time with "X" type stitches.

Two days after this closure a skin-covered evisceration took place. The decision of performing a new surgery to repair the evisceration was made. At this time, the primary closure of the abdominal wall was impossible, so the surgeons decided to put a 25 x 15 cm Polyglactin mesh as a bridge. The intra-abdominal pressure in this moment was 12,3 mmHg.

A month later, the skin and subcutaneous tissue suture failed and the abdominal closure became a laparostomy with granulation tissue. In addition, the patient developed a new intra-abdominal leak that was conducted to the skin with a drain (Fig. 3).

At this moment, the patient was referenced to us. We decided to employ the NPWT (Fig. 3). Fifteen days later we decided to perform a new surgery to close the mid-line, achieve a better drainage of the leak of the jejunojejunostomy and place a feeding catheter at the distal loop (Fig. 4).

After this procedure, we faced an entero-atmospheric fistula and we considered some different options to manage it in the (Fig. 5).

### *A. T-DRAIN*

Placing a T-drain (red color in the (Fig. 5)) into both loops of the fistula (proximal and distal). This option allows us to keep the nutrition tube in the distal loop. Then, we should place the black sponge polyurethane with an abdominal foil

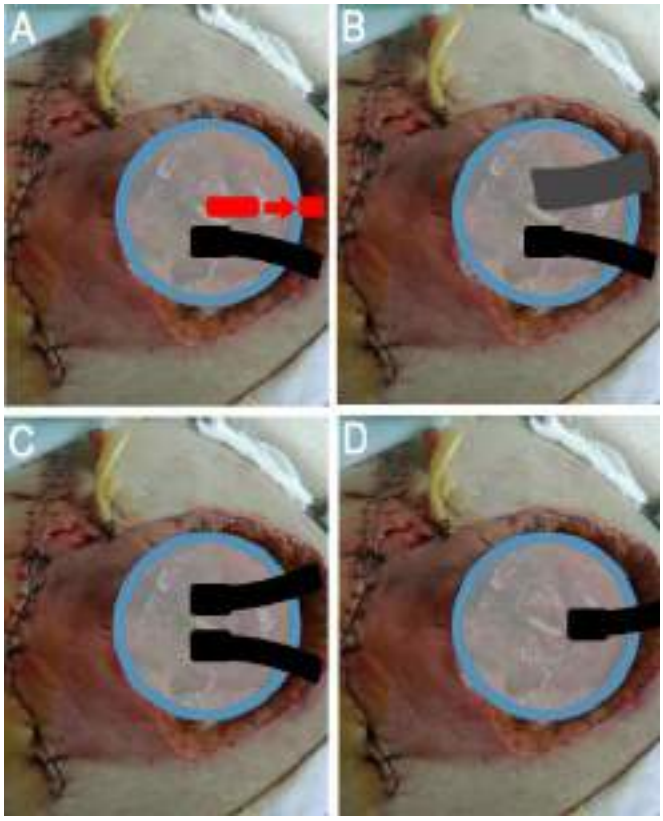


Figure 5. Surgical management options of the fistula: A: T-drain and NPWT. B: Stoma bag and NPWT C: Two NPWT ports. D: NPWT port directly on the fistula

below (on the intestines surface). The T-drain should go through the sponge and we should put some stoma paste around the sponge (blue color at the (Fig. 5), especially in the lowest part and in damaged skin. Finally, we should place the adhesive on the surface (the drain needs to go through it) and cut the hole in the adhesive for the port (preferably in the lowest part of dressing). We should connect the T-drain to the normal suction with low pressure (too high pressure may increase the secretion and may also lead to the closure of the drain if it is elastic) and the port into NPWT system (Fig. 5).

### *B. STOMA BAG*

Placing the abdominal foil on the surface of intestines with a hole above the fistula. After placing the black sponge on the wound, surrounded by the stoma paste, cut an opening in the sponge right above the fistula (the diameter should be not too small, 6-7 cm), and put stoma paste around it. We should cut the hole in the foil above the fistula, with a diameter of about 3-4 cm. Cut the hole for NPWT drain. Use a stoma bag above the fistula opening and connect the NPWT port (Fig. 5).

### *C. TWO NPWT PORTS*

It consists of placing the abdominal foil on the surface of the intestines with a hole above the fistula. A ring of stoma

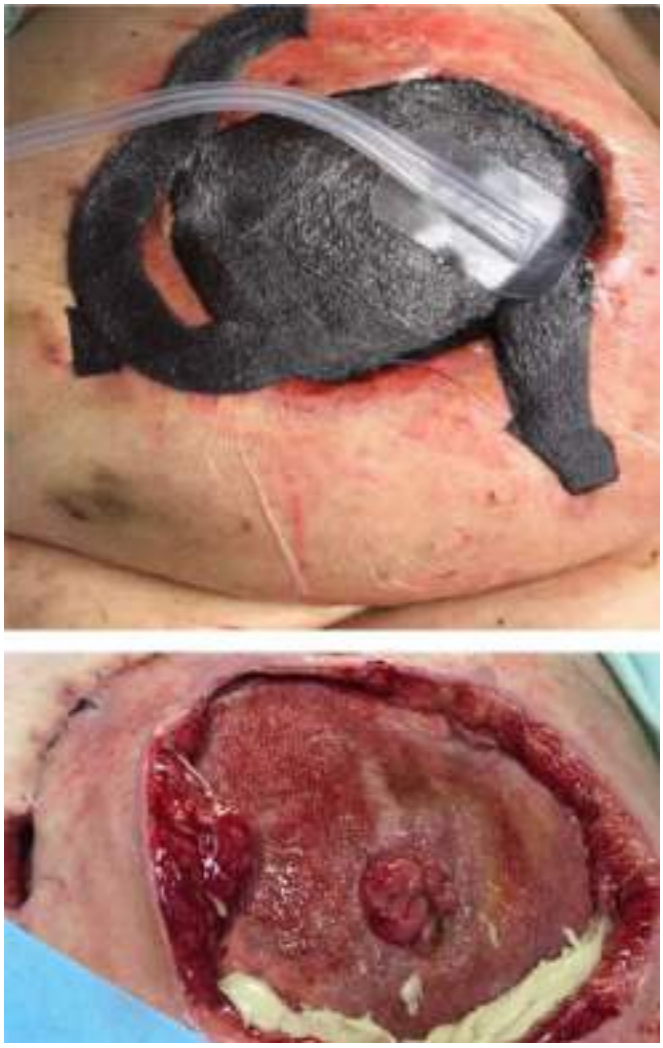

Figure 6. The NPWT dressing with the port directly on the fistula.

paste should be placed above the fistula, leaving an opening around it, minimum 5 cm of width. We should place the black sponge with stoma paste around it. It is necessary to make the sponge thinner above the fistula. We should cut two openings for the NPWT ports and connect them with NPWT. The lowest port (on the wound surface) should have a negative pressure around 125 mmHg. After 3 -6 days we should try to change pressures: the lowest above the fistula and the highest applied to the tissue around (Fig. 5).

### *D. NPWT PORT DIRECTLY ON THE FISTULA*

We chose this option. We first placed the abdominal foil on the surface of the intestines with a hole above the fistula, with a ring of stoma paste (leaving an opening around it, minimum 5 cm width). Then we placed the polyurethane sponge with a hole above the fistula with a ring of stoma paste. Finally, we put the adhesive foil on the surface with a hole above the fistula and we connected the port of the NPWT system in this hole (Fig. 6)(Fig. 7). On the one hand, the patient required a change of the dressing every 12-24 hours being it very complex. Initially, We did not achieve the management of

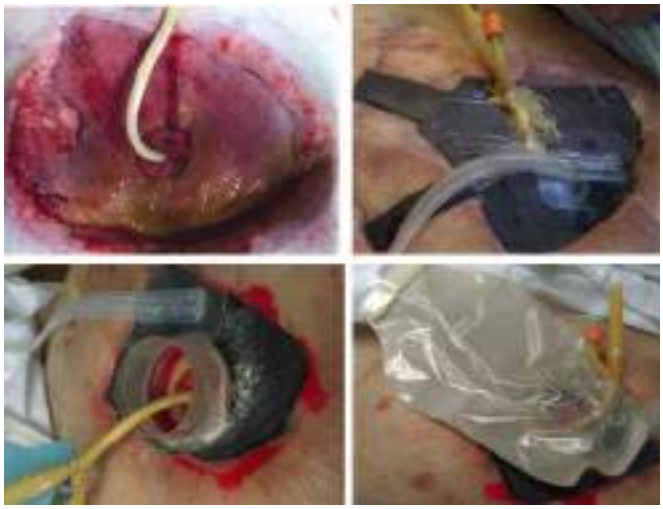

Figure 7. The NPWT dressing adapted with the catheter for feeding and the urine jar as a collector.

Figure 8. The evolution from the laparostoma to the entero-atmospheric fistula and the improvement of the granulation tissue almost becoming a stoma around the fistula.

the intestinal fluids, the bile accumulated on the healing bed of granulation tissue and was creating an important damage and skin irritation. On the other hand, it was difficult to keep the feeding catheter while we were applying this kind of dressing (Fig. 7). In order to prevent the accumulation of the bile, we placed an urine jar as a collector, but this accessory made the dressing more complex (Fig. 8). We can see the notorious improvement using the NPWT during two months (four months since the first surgery)(Fig. 9). At this moment we had achieved the goal of managing the laparostoma and of the entero-atmospheric fistula, but we could not ensure a continuous nutritional support for the patient.

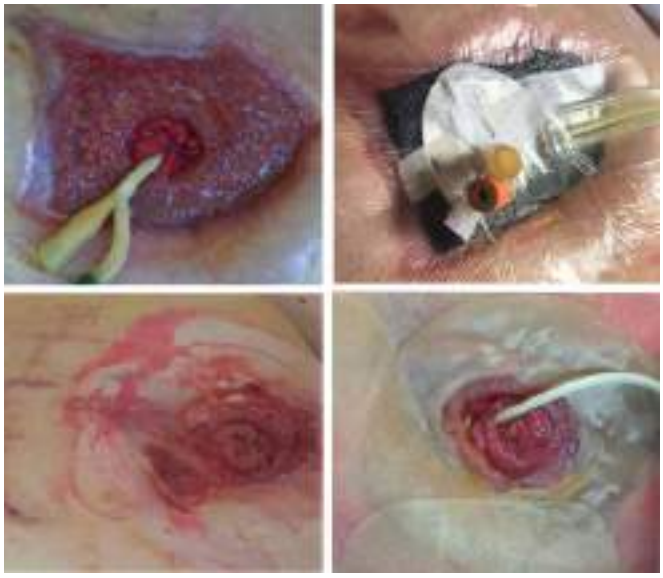

Figure 9. Last days of NPWT.Pictures of the dressing after NPWT.

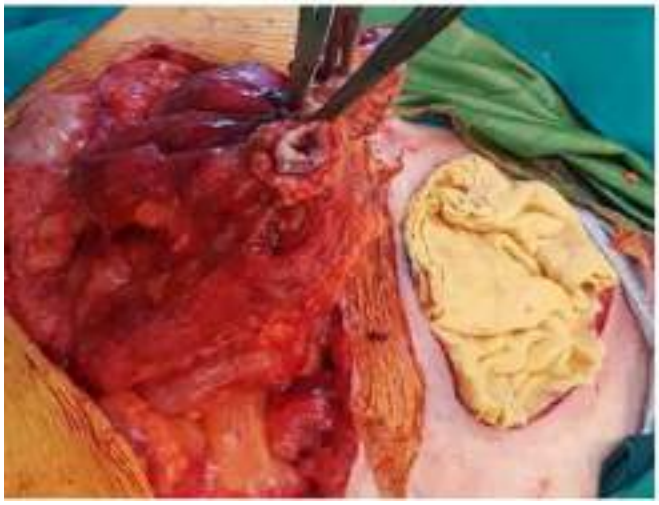

Figure 10. Adhesions between the graft and the underlying bowel.

In this situation, even though it is known that the indication of the definitive closure of the fistula should be made after 6-12 months of its appearance (in order to reduce the risk of intestinal injury), we decided to perform an operation to restore the gastrointestinal continuity. It was long time that the patient was feeding with the parenteral nutrition (with the subsequents hepatic alterations), because we could not get an enteral feeding with a catheter at the distal loop: at the beginning, the reason was the negative pressure that made the enteral feeding go out from the wound, and later, the difficult control of the infusion of enteral feeding with the bomb. Because all of these reasons we decided to come ahead of time with the surgery. We found adhesions between bowels and between the graft and the underlying bowel (Fig. 10). The three intestinal limbs of the Roux-en-Y-anastomosis were adhered to the abdominal wall, so we performed a section of each one (5 cm) followed by a new manual anastomosis. The alimentary limb became 1 m long, the biliary limb 40

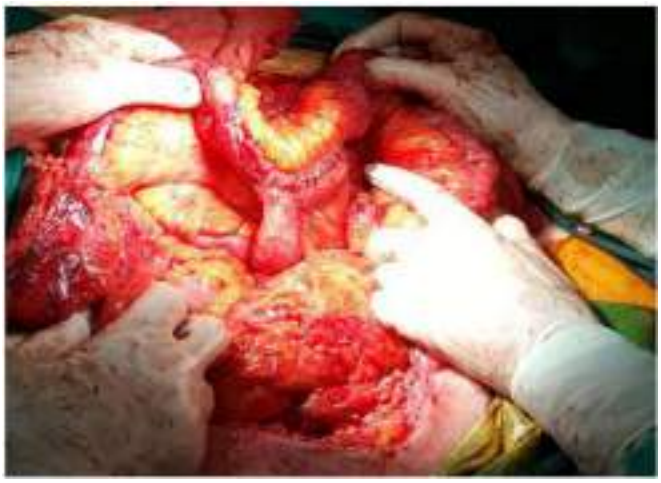

Figure 11. Picture of the three intestinal limbs with adhesions to the abdominal wall on the fistula. We sectioned these adhesions before performing the section of the three limbs

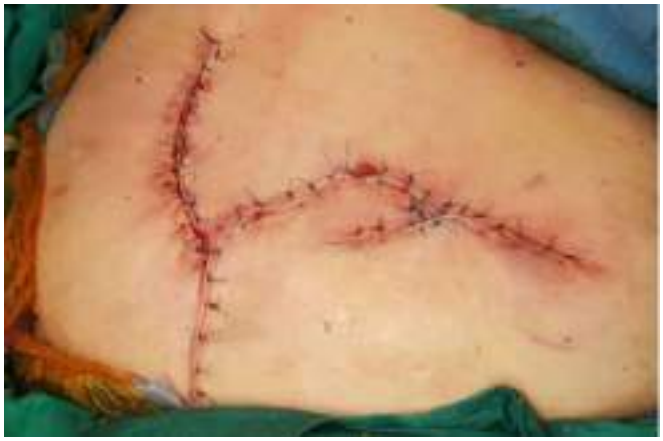

Figure 12. Result after the surgery.

cm and the distal limb 1.40 m long (Fig. 11). Once the fistula is resected and gastrointestinal continuity restored, the abdomen should be closed using standard techniques, provided this will not result in undue tension. We carried out a skin subcutaneous tissue approximation with advancement flaps (Fig. 12).

## III. DISCUSSION

Vacuum-assisted closure (VAC), sometimes referred to as microdeformational wound therapy (MDWT) or negative pressure wound therapy (NPWT), has revolutionized wound care over the last 15 years. When using NPWT devices significant shrinkage of the wound can be observed as the wound edges come together by a combination of foam shrinkage and drawing the edges of the wound together by foam contact. At the wound interface, the foam creates microdeformations that stretch cells and activate molecular pathways for angiogenesis and cell division. For wounds with oedema, these devices have the capacity to remove a large amount of fluid.[6]

NPWT can be very useful for the management of entero-atmospheric fistula.[7] Continuous suction of the fistula output minimizes contact time between intestinal fluid and exposed peritoneum, thus effectively controlling intestinal spillage. Patients with entero-atmospheric fistula who have failed five to six weeks of nonoperative management will likely need surgery to definitively manage the fistula. Although the timing of definitive surgery to close the fistula is a matter of judgment, once it has been determined that the fistula is not likely to resolve on its own, surgery should generally not be undertaken for another few months to lessen the risk of bowel injury.[8] Imaging should be repeated to ensure that fluid collections are drained, and inflammation has resolved. Dense adhesions begin to form in the open abdominal wound after approximately one week of exposure and remain treacherous for at least six to eight weeks. The presence of a fistula is usually associated with a severe the inflammatory response that leads to dense adhesions, known as “obliterative peritonitis”, that make early surgery hazardous.[9, 10] buy and sell usd In addition to issues related to adhesion formation, definitive management of an enteroatmospheric fistula should not be considered until the skin graft is supple and can be pinched between the thumb and index finger, which signifies the existence of a plane between the graft and underlying bowel.[11] This signifies that there is a tissue plane between the skin graft and the gut, facilitating one of the more difficult steps of abdominal wall reconstruction, which is dissection of the skin graft off the bowel. The aim of surgery is to eliminate the fistula, which usually requires resection of the a segment of bowel that is the origin of the fistula, reestablishment of gastrointestinal continuity, and tension-free closure of the abdomen with well-vascularized soft tissue.[12]

Once the fistula is resected and gastrointestinal continuity restored, the abdomen should be closed using standard techniques, provided this will not result in undue tension. The goal of the definitive surgery in the management of entero-atmospheric fistula, besides closing the fistula, is to reconstruct the abdominal wall with durable well-vascularized tissue. A two-team approach has the advantage of providing a well-rested plastic surgeon focused on reconstruction after a long and tedious visceral dissection by the general surgery team.[12] Closure of large or complex abdominal wall defects associated with entero-atmospheric fistulas may require advancement flap techniques. One option for abdominal closure is the component separation technique, provided the rectus abdominis muscle remains intact.[13] Defects up to 10 cm in the upper abdomen, 20 cm in the mid-abdomen, and 8 cm in the lower abdomen can be closed using this technique. Other options may include random, pedicle, or free flaps with microvascular reconstruction.

## IV. CONCLUSION

The application of NPWT in the management of entero-atmospheric fistula is a widely accepted therapeutic method. NPWT has many beneficial clinical effects : it creates a moist environment, improves fluid removal, reduces tissue edema, contracts the wound mechanically stimulates the wound bed, induces cell proliferation, alters blood flow to the wound edges stimulates neoangiogenesis and the formation

of granulation tissue. In our case, applying NPWT allowed turning an entero-atmospheric fistula into a stoma around the fistula. However, it is important to remember that patients with entero-atmospheric fistula who have failed five to six weeks of nonoperative management will likely need surgery to definitively manage the fistula.

## V. Acknowledgement

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# Management of large chronic venous leg ulcers with negative pressure wound therapy

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**CASE REPORT**

***Abstract*—Introduction: Venous leg ulcers (VLU) occur in 1% of the adult population and are associated with chronic disability, diminished quality of life and high health-care costs. Treatment is often slow, difficult and recurrence is high because of inappropriate conditions of the wound bed.**

**Patients and Methods: This study involves 14 patients with chronic venous ulcers larger than 100 cm$^2$ treated with negative pressure wound therapy (NPWT). Patients underwent a radical debridement of all devitalized tissues and partial stripping of an insufficient great saphenous vein in the first operation. After adequate haemostasis, NPWT kit was applied. Once the wounds were determined to be clean and adequate granulation tissue formation was achieved, split-thickness skin grafts were applied. Dressing impregnated with neutral triglycerides and silver ions was used as a first layer and the black polyurethane NPWT foam was applied over it. The pain assessment was performed for 7 patients using 10 cm visual analog scale (VAS).**

**Results: The mean number of NPWT dressing changes prior to grafting was 5.8. The mean number of NPWT foam changes was 2.8 after skin grafting. We accomplished complete healing of 92% of applied skin grafts surface. One patient had recurrence of venous ulcers in the follow-up period. Moreover, one patient required regrafting.**

**Conclusions: The application of NPWT provides quick wound-bed preparation and high graft take in venous ulcer treatment.**

***Keywords*—venous ulcers, negative pressure wound therapy, chronic wound, chronic venous insufficiency, skin graft, silver, pain**

## I. Introduction

THE venous leg ulcers (VLU) occur in 1% of adult population and are associated with chronic disability, diminished quality of life and high health-care costs. Chronic venous insufficiency is the main cause of venous ulcers development.[1] Increased pressure in the venous system lead to elevated pressure in the capillaries. That allows large molecules and cells to escape into the interstitial fluid. Accumulation of blood cells and fibrinogen deposits inhibits collagen production and plugging the capillaries which lead to tissue ischaemia. Secretion of growth factors, cytokines and matrix metalloproteinases is deregulated. All these unfavourable factors disrupts the skin's microcirculation, stimulate inflammation and create a non-healing environment.[2] Treatment is often slow, difficult and challenging. Poor prognostic factors include large size of the ulcer and prolonged duration. Moreover, the recurrence rates may be as high as 70%.

The best clinical outcomes are achieved through a multimodal care pathway, which includes nutrition, debridement, vascular surgical intervention and compression therapy along with advanced wound management.[3, 4]

The negative pressure wound therapy (NPWT) also known as the vacuum-assisted closure (VAC) is very fast developing method of the wounds treatment. It perfectly executes TIME rule (T- tissue debridement, I- infection and inflammation control, M - moisture balance and E -epidermalization stimulation). The beneficial effects of NPWT on the wound healing include: mechanical drainage, moist environment, reduction of swelling, stimulation of granulation tissue formation, increase in local blood, neoangiogenesis, reduction of bacterial colonization.[5]

## II. Patients and Methods

From March 2012 to December 2015, 31 patients with chronic venous ulcers were treated with NPWT at the Department of General Surgery, John Paul II Memorial Hospital in Bełchatów. The venous origin of the ulcer was confirmed by the venous Doppler sonography and ABI measurement. Patients with diabetic or ischaemic ulcers and patients with arterial insufficiency of the lower extremity (ABI <0,9) were not included in the study. Finally, 14 patients with venous ulcers larger than 100 cm$^2$ were qualified to the retrospective analysis. The cultural swab was taken from ulcers on the admission day. The antibiotics were administered according to culture and susceptibility test results. The surface of wound was measured by projection of the ulcers onto transparent foil with preprinted 1cm$^2$ measures. Half/squares were rounded up to 1cm$^2$.

At the beginning of hospital stay, crossectomy and partial stripping of insufficient great saphenous vein (up to ulcer level) were performed in all patients. The insufficient perforator veins were also ligated if detected. Moreover all patients underwent a radical debridement of all necrotic tissues, fibrin

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Table I
CHARACTERISTICS OF THE PATIENTS

| | Patient Age | Sex | Duration of the ulcer (years) | Surface of the ulcer [$cm^2$] | Number of NPWT dressing changes prior to grafting | Number of NPWT dressing changes after grafting | Percentage of vital surface of mesh grafts |
|---|---|---|---|---|---|---|---|
| 1 | 58 | F | 3 | 220 | 6 | 2 | 99 |
| 2 | 60 | F | 4 | 345 | 5 | 2 | 95 |
| 3 | 75 | F | 20 | 180 | 3 | 4 | 98 |
| 4 | 50 | F | 10 | 270 | 10 | 3 | 90 |
| 5 | 69 | M | 7 | 320 | 8 | 3 | 90 |
| 6 | 70 | M | 5 | 110 | 6 | 2 | 93 |
| 7 | 58 | M | 6 | 105 | 4 | 2 | 99 |
| 8 | 62 | M | 3 | 150 | 8 | 4 | 88 |
| 9 | 73 | F | 1 | 110 | 3 | 3 | 9 |
| 10 | 56 | F | 2 | 135 | 3 | 3 | 95 |
| 11 | 67 | M | 3 | 120 | 5 | 2 | 90 |
| 12 | 59 | F | 4 | 720* | 9 | 3 | 96 |
| 13 | 80 | F | 1 | 280 | 5 | 3 | 95 |
| 14 | 60 | F | 1 | 190 | 6 | 3 | 70 |

* venous ulcers of both legs

deposits and ointment remained during the first operation (Fig. 1)A,B (Fig. 2)A (Fig. 4)A,B. The polyurethane foam (VivanoMed Foam, PAUL HARTMANN AG, Germany) was applied to the ulcer and the pump was set to a continuous negative pressure of -120 mm Hg. Dressings were changed every second day. To improve patient comfort during the dressing change — 1% lidocaine was administered into the foam 30 minutes earlier. After 48 hours, the pressure mode was switched to intermittent negative pressure at -120 mmHg/-20 mmHg. Once the wounds were determined to be clean by clinical assessment and adequate granulation tissue formation was achieved — the meshed split-thickness skin grafts (SGTS) were applied (Fig. 1)C,D (Fig. 2)B (Fig. 3)B (Fig. 4)C. The Atrauman AG (non-adherent, polyester tulle, impregnated with neutral triglycerides and silver ions, PAUL HARTMANN AG, Germany) was used as a primary dressing for skin grafts and covered with NPWT dressing kit with continuous negative pressure of 75–100 mm Hg (Fig. 1)E,F. The NPWT dressings were changed on the third day after grafts application. We removed only polyurethane foam, however, the primary dressing (Atrauman AG) remained untouched. The whole dressing (NPWT and polyester tulle with silver ions) was changed on 5th or 6th day after grafts application. Negative pressure wound therapy was continued until it was considered that the grafts uptake was complete (Fig. 1)G (Fig. 2) C (Fig. 3)C (Fig. 4)D.

The pain assessment was performed for 7 patients using 10 cm visual analog scale (VAS). The third-class medical compression stockings were recommended upon patient's' release from the hospital. The patients were examined on monthly follow-up visits after discharge. (Fig. 1)H (Fig. 2)D(Fig. 3)D.

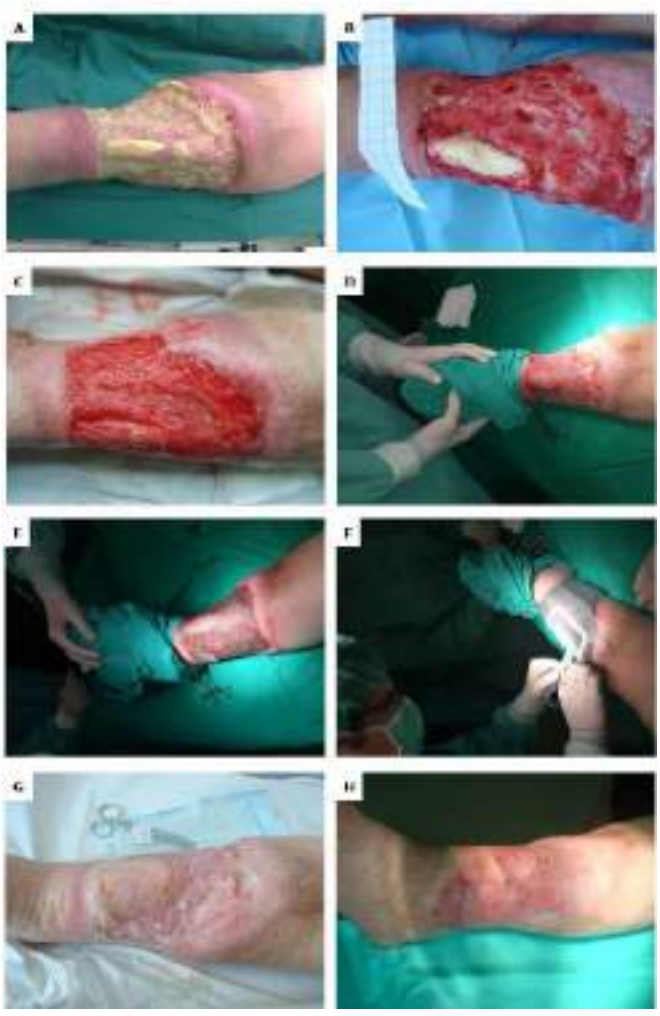

Figure 1. Patient no. 4 in Table 1; a) the wound at the moment of admission; b) the wound after debridement; c) the wound bed filled with granulation tissue after 20 days of NPWT; d,e,f) application of meshed split-thickness skin grafts covered with silver impregnated dressing and NPWT; g) the wound at the moment of discharge from the hospital; h) the wound 3 months after discharge from the hospital;

## III. RESULTS

We treated 14 patients (9 women and 5 men) with venous ulcers larger than 100 $cm^2$. A mean age of the patients was 64.07 years (range 56–80 years). The ulcer surface area was from 105 $cm^2$ to 720 $cm^2$ (one patient had ulcerations on

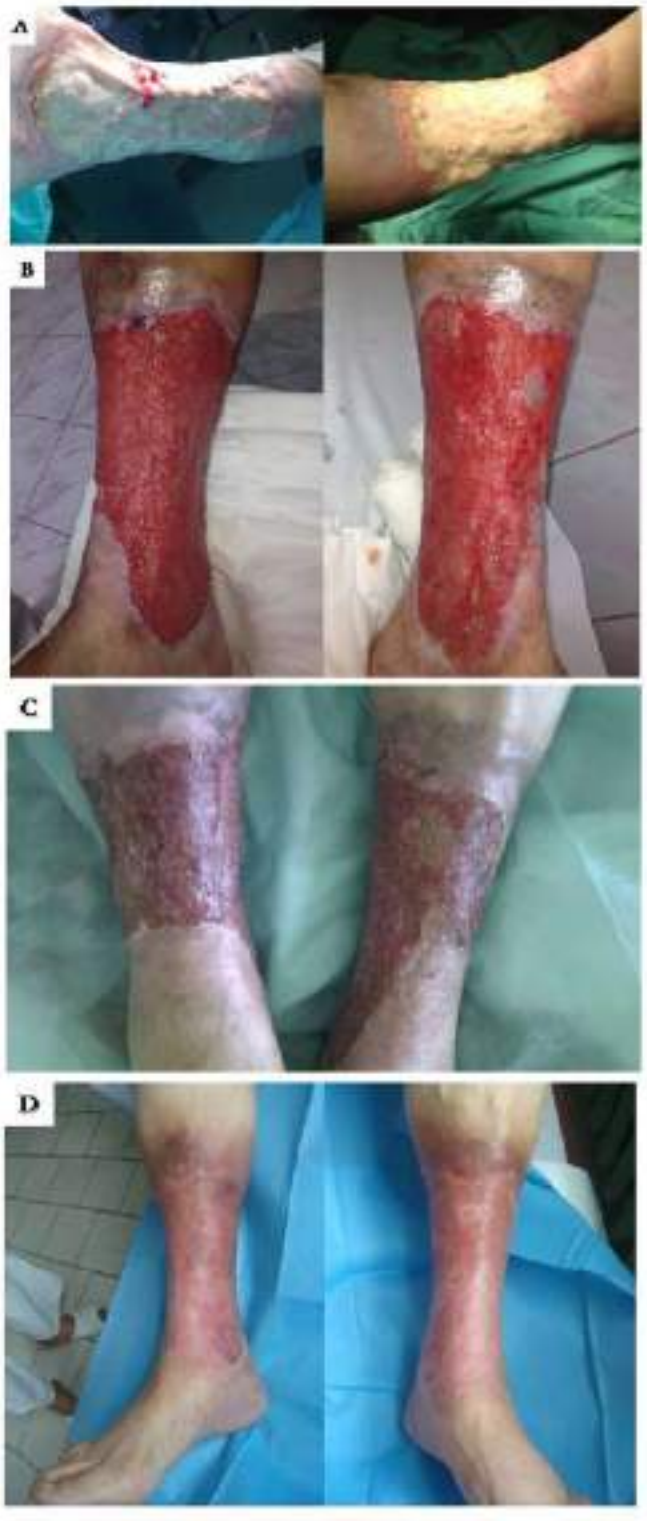


Figure 2. Patient no. 12 in Table 1; a) wounds of both legs at the moment of admission; b) the wounds bed filled with granulation tissue after 20 days of NPWT; c) the wounds at the moment of discharge from the hospital; d) the wound 2 months after discharge from the hospital

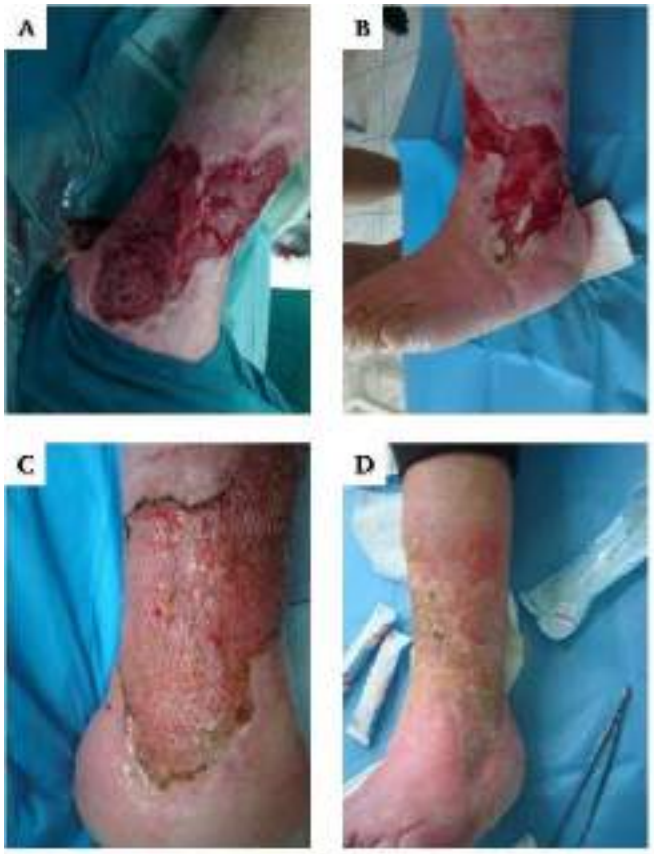


Figure 3. Patient no. 11 in Table 1; a) the wounds at the moment of admission; b) the wound bed filled with granulation tissue after 6 days of NPWT; c) the wounds at the moment of discharge from the hospital; d) the wound 3 months after discharge from the hospital

both legs). The mean ulcer duration prior to admission to our ward was 5 years (range 1-20 years). The mean number NPWT dressing changes prior to skin grafting were 5.8 (3-10 changes) and 2.8 after grafting (2-4 changes). (Tab. I)

All patients reported a little higher pain level during therapy compared with their pain level before treatment and much higher during dressing change so then they required additional painkillers. The pain level decrease during hospitalization even when the foam was changed. (Tab. II)

One patient had recurrence of venous ulcers 2 months after discharge from the hospital. One patient required regrafting due to only 70 % take rate of SGTS (Fig. 4)E.

## IV. Discussion

Experience of vacuum therapy used in medicine has a long history and dates back to the ancient times. However important milestone in vacuum application was introduced by the German surgeon Bier and later by his student Klapp at the beginning of 20th century. Their suction pump was used for removal of the infectious materials in acute inflammatory diseases of the soft tissue and the purulent wounds or diabetic gangrene of feet. The negative pressure therapy for the treatment of wounds was popularized by Argenta and Morykwas in 1997, who described the use of subatmospheric

pressure through a suction applied to polyurethane foam to improve wound healing.[6]

The accurate mechanism of the NPWT action is not clear however it gives the number of beneficial clinical effects. It facilitates wound cleansing, creates a moist environment, establishes the fluid balance by removal of the exudate from the wound, reduces the tissue edema, contracts the wound, mechanically stimulates the wound bed, improves microcirculation, stimulates angiogenesis and the formation of granulation tissue, reduces bacterial load and the risk of infection.[7–11]

The application of the topical negative pressure therapy has been shown to accelerate debridement and promote healing in many different types of wounds.[12] Lore' e et al. applied the vacuum-assisted closure to improve the quality of the wound bed in VLU and they noticed that the median percentage reduction in fibrinous tissue was 28% on day three and 40% on day six of therapy.[13] Vuerstaek et al. in a randomized controlled trial showed that the negative pressure was able to prepare wound bed of venous ulcer significantly faster for surgical closure than in the control group. Moreover, costs of conventional wound care were higher than those of NPWT therapy.[14]

Table II
PAIN LEVEL DURING NPWT

| Pain level on VAS scale (average for 7 patients) | Time of therapy |
|---|---|
| 3,1 | Moment of admission; |
| 3,9 | During NPWT, at the beginning of therapy; |
| 6,3 | During dressing change, at the beginning of NPWT therapy; |
| 3,4 | During NPWT, at the end of therapy; |
| 5,6 | During dressing change, at the end of therapy; |

According to the International Expert Panel on Negative Pressure Wound Therapy (NPWT-EP) recommendations — if compression therapy is not efficacious, the NPWT should be used to prepare the wound for surgical closure or to progress to wound closure by secondary intention.[12]

Following wound bed preparation, closure of venous leg ulcers is commonly carried out by skin grafting. The benefits of NPWT to support skin grafts in different types of wounds were repeatedly reported[15–18] as well as in venous ulcers.[19] The NPWT demonstrated increase in grafts take rate and improvement in graft quality. Thanks to the negative pressure, the graft adheres to its bed strictly, and interstitial edema resulting from the venous insufficiency is effectively removed. The results of study performed by Korber et al. revealed complete healing in 92.9% of meshed grafts in which they had applied VAC compared to 67.4% in the control group without postoperative VAC therapy.[20] Similar improvement was reported by Vuerstaek.[14]

In our study, we used polyester tulle, impregnated with neutral triglycerides and silver ions as a primary dressing for skin grafts. The usefulness of silver as an antimicrobial agent has been known since antiquity and is well established.[21] The antimicrobial effect of silver is mediated by the presence of the highly reactive $Ag^+$ cation which is disruptive to many aspects of microorganism metabolism. The mechanism of action includes damage to the bacterial cell wall, blockage of transport and enzyme systems such as the respiratory cytochromes, alteration of proteins and binding of microbial deoxyribonucleic acid and ribonucleic acid to prevent transcription and division.[22] Silver is regarded as a broad-spectrum agent and shows activity against the pathogens such as *Stapylocoocus aureus* and *Pseudomonas spp.*, which frequently colonizes chronic venous ulcers.[23]

Despite its advantages in treating infected wounds, silver has been demonstrated to be cytotoxic to human keratinocytes and fibroblasts in vitro.[21, 24] However, the clinical correlation to support this finding remains unclear.[22, 25] Some authors suggest that the human body has complex homeostatic mechanisms and silver might have different effects in vivo than in vitro.[22, 26] However, we believe that antimicrobial characteristics of silver ions preponderate its cytotoxic effect. We tried to combine beneficial effect of Ag cations with advantages of VAC therapy. This strategy seems to be promising because we accomplished complete healing of 92% of applied skin grafts surface. Hence, randomized control group studies will be necessary to confirm these hypothesis. Pain is a common side effect of NPWT affecting quality of life and even precluding some patients from continuing with the treatment. Many studies reported significantly higher pain levels during therapy compared with their pain levels before treatment.[27–29] Moreover, high sensation is experienced during dressing change, especially in foam-based NPWT. It may be due to wound bed disruption and mechanical tissue damage when the foam and adhering tissue are torn from the wound bed [30]. One method that has been described to reduce pain is to replace the foam with the gauze. In a randomized study comparing gauze-based and foam-based NPWT, Dorafshar et al. reported that gauze-based NPWT provides a less painful option compared with foam-based NPWT.[30]

This may be due to the lack of tissue ingrowth observed with gauze. Similar observations were made by Fraccalvieri et al.[31] Researchers from Sweden compared the expression of calcitonin gene-related peptide (CGRP) and substance P in the wound bed following NPWT and foam or gauze dressing removal. CGRP and substance P are neuropeptides that cause inflammation and signal pain and are known to be released when tissue trauma occurs. The results of study show that both peptides were more abundant in the wound edge after the removal of foam than the removal of gauze after NPWT.[32]

According to NPWT-EP recommendations, gauze may be chosen in patients more susceptible to pain and may be a means of reducing pain experienced during dressing removal.[12] Another way to reduce pain reported by the patients during the dressing change is the installation of anesthetic through the suction tubing 30 minutes before. In two double-blind, randomized studies topical lidocaine application was associated with lower score on the 0-10 visual analog scale for pain during the NPWT sponge removal.[33, 34] Some researchers have suggested that NPWT is not more

painful than conventional dressing. Randomised controlled trial performed by Vuerstaek et al. evaluated outcome in leg ulcer patients receiving NPWT or conventional wound care techniques. The pain levels were found to be similar in both groups during the first 5 weeks of therapy, however, those who received NPWT reported significantly less pain after the fifth week. Authors suggest that although NPWT may be just as painful as other wound treatments, the pain may be less prolonged and only short-term.[14]

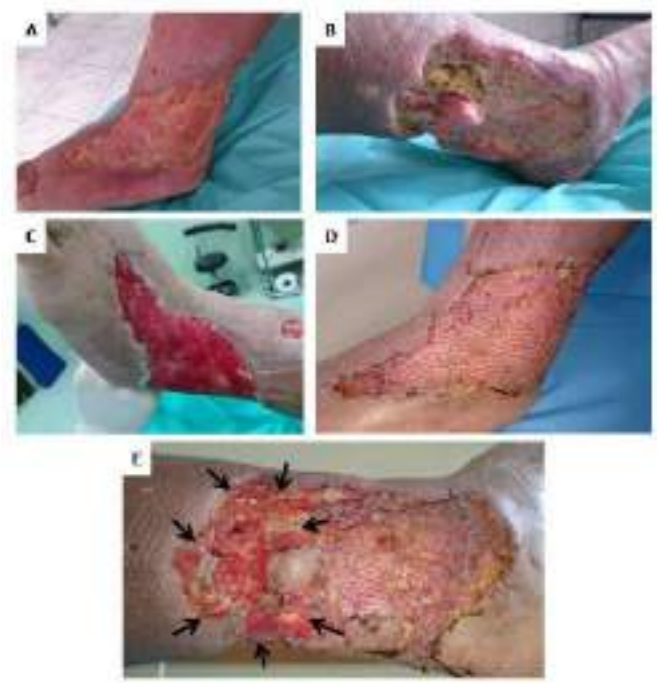

Figure 4. Patient no. 14 in Table 1; a,b) the wounds at the moment of admission; c) the wounds bed filled with granulation tissue after 13 days of NPWT; d, e) healing of only 70 % of applied skin grafts, regrafting was needed on the marked area (black arrows).

## V. Conclusions

This study describes effective and efficient use of NPWT in the treatment of huge chronic venous ulcers. The limitation of our study is the lack of control group and the small number of patients. Application of negative pressure wound therapy provided quick wound-bed preparation for surgical closure. Moreover, the NPWT stimulates the process of anastomosis creation between bed and the graft vessels and removes the exudate that may hamper graft's adhering. What are more the bacteria that impair wound healing are eradicated by the antimicrobial properties of silver impregnated dressings? Therefore the NPWT combined with silver dressings demonstrates an increase in graft take rate and improvement in graft quality. Finally, that significantly reduces the time and costs of wound treatment.

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U pacjentów z zaburzeniami czynności nerek: Dostosowywanie dawki nie jest konieczne u pacjentów z łagodnymi lub umiarkowanymi zaburzeniami czynności nerek (klirens kreatyniny 30 ml/min do 79 ml/min). Dostosowywanie dawki nie jest konieczne u pacjentów regularnie poddawanych hemodializie (3 razy w tygodniu); dalbawancyna może być podawana bez względu na czas hemodializy. U pacjentów z przewlekłymi zaburzeniami czynności nerek, u których klirens kreatyniny wynosi <30 ml/min i którzy nie są regularnie poddawani hemodializie, zalecany schemat dawkowania dalbawancyny raz w tygodniu należy zmniejszyć do dawki 750 mg, a następnie po tygodniu o 375 mg. U pacjentów z zaburzeniami czynności wątroby: Dostosowywanie dawki dalbawancyny nie jest zalecane u pacjentów z łagodnymi zaburzeniami czynności wątroby (stopień A w klasyfikacji Childa-Pugha). Należy zachować ostrożność, przepisując dalbawancynę pacjentom z umiarkowanymi lub ciężkimi zaburzeniami czynności wątroby (stopień B i C w klasyfikacji Childa-Pugha), ponieważ nie ma danych umożliwiających określenie właściwego dawkowania. Dzieci i młodzież: Nie określono jeszcze bezpieczeństwa ani skuteczności stosowania dalbawancyny u dzieci w wieku od urodzenia do poniżej 18 lat. **Sposób podania:** *Podanie dożylne.* Produkt leczniczy Xydalba musi być odtworzony, a następnie rozcieńczony przed podaniem w infuzji dożylnej przez 30 minut. Należy zapoznać się z instrukcją dotyczącą odtwarzania i rozcieńczania tego produktu leczniczego przed podaniem. **Przeciwwskazania:** Nadwrażliwość na substancję czynną lub na którąkolwiek substancję pomocniczą (mannitol (E421), laktoza jednowodna, kwas solny (do ustalenia pH), sodu wodorotlenek (do ustalenia pH)). **Specjalne ostrzeżenia i środki ostrożności dot. stosowania:** Reakcje nadwrażliwości: Produkt leczniczy Xydalba należy z ostrożnością podawać pacjentom, o których wiadomo, że są nadwrażliwi na inne glikopeptydy, ze względu na możliwość wystąpienia krzyżowej nadwrażliwości. Jeżeli wystąpi reakcja alergiczna na produkt leczniczy Xydalba, należy przerwać jego podawanie i zastosować właściwe leczenie reakcji alergicznej. Biegunka spowodowana przez *Clostridium difficile*: Podczas stosowania prawie wszystkich antybiotyków obserwowano związane z leczeniem przeciwbakteryjnym zapalenie okrężnicy i rzekomobłoniaste zapalenie okrężnicy, których przebieg może być od łagodnego do zagrażającego życiu. Z tego względu należy brać pod uwagę to rozpoznanie u pacjentów z biegunką występującą podczas lub po zakończeniu leczenia dalbawancyną. W takich przypadkach należy rozważyć przerwanie podawania dalbawancyny i zastosowanie leczenia wspomagającego oraz specyficznego dla zakażenia *Clostridium difficile*. U tych pacjentów nigdy nie należy stosować produktów leczniczych tłumiących perystaltykę. Reakcje związane z infuzją: Produkt leczniczy Xydalba podaje się w infuzji dożylnej, z wykorzystaniem całkowitego 30-minutowego czasu trwania infuzji, w celu zminimalizowania ryzyka reakcji związanych z infuzją. Szybkie infuzje dożylne przeciwbakteryjnego glikopeptydu mogą przyczynić się do wystąpienia reakcji przypominających „zespół czerwonego człowieka", który obejmuje nagłe zaczerwienienie górnych części ciała, półrzywę, świąd i (lub) wysypkę. Zaprzestanie podawania infuzji lub jej spowolnienie może spowodować ustąpienie tych reakcji. Zaburzenia czynności nerek: Informacje dotyczące skuteczności i bezpieczeństwa stosowania dalbawancyny u pacjentów, których klirens kreatyniny wynosi <30 ml/min są ograniczone. Na podstawie opinekcji, dostosowywanie dawki jest konieczne u pacjentów z przewlekłymi zaburzeniami czynności nerek, u których klirens kreatyniny wynosi <30 ml/min i którzy nie są regularnie poddawani hemodializie. Zakażenia mieszane: W przypadku zakażeń mieszanych, jeśli się podejrzewa obecność bakterii Gram-ujemnych, pacjentów należy leczyć odpowiednimi lekami przeciwbakteryjnymi działającymi na bakterie Gram-ujemne. Drobnoustroje niewrażliwe: Zastosowanie antybiotyków może promować namnażanie drobnoustrojów niewrażliwych. Jeżeli podczas terapii wystąpi nadkażenie, należy wdrożyć odpowiednie postępowanie. Ograniczenia danych klinicznych: Dane dotyczące bezpieczeństwa stosowania i skuteczności dalbawancyny w przypadku zastosowania więcej niż dwóch dawek (w odstępie jednego tygodnia) są ograniczone. W kluczowych badaniach w przypadku ABSSSI rodzaje leczonych infekcji były ograniczone jedynie do cellulitis/ropni, ropni i infekcji ran. Brak doświadczenia dotyczącego stosowania dalbawancyny w leczeniu pacjentów z silnie obniżoną odpornością. **Ciąża i laktacja:** Nie ma danych dotyczących stosowania dalbawancyny przez kobiety w ciąży. Badania na zwierzętach wykazały toksyczne działanie na reprodukcję. Xydalbarnie jest zalecana w okresie ciąży, o ile nie jest to bezwzględnie konieczne. Nie wiadomo, czy dalbawancyna przenika do mleka matki (mleka ludzkiego). Niemniej dalbawancyna przenika do mleka samic szczurów karmiących piersią i może również przenikać do mleka ludzkiego. Dalbawancyna nie wchłania się dobrze po podaniu doustnym, niemniej nie można wykluczyć wpływu dalbawancyny na florę żołądkowo-jelitową oraz florę jamy ustnej karmionego piersią niemowlęcia. Należy podjąć decyzję o kontynuacji/zaprzestaniu karmienia piersią lub kontynuacji/zaprzestaniu leczenia produktem Xydalba, biorąc pod uwagę korzyści z karmienia piersią dla niemowlęcia oraz korzyści z terapii dla kobiety. Płodność: Badania na zwierzętach wykazały obniżoną płodność. Potencjalne ryzyko, na które narażeni są ludzie jest nieznane. **Działania niepożądane:** Podsumowanie profilu bezpieczeństwa: W fazie 2/3 badań klinicznych dalbawancynę otrzymało 2473 pacjentów. Była ona podawana albo w infuzji jako dawka pojedyncza 1500 mg, albo w dawce 1000 mg, a następnie po tygodniu w dawce 500 mg. Najczęściej występującymi działaniami niepożądanymi występującymi u ≥1% pacjentów leczonych dalbawancyną były: nudności (2,4%), biegunka (1,9%) oraz ból głowy (1,3%), i zwykle miały lekkie lub umiarkowane nasilenie. Tabelaryczny wykaz działań niepożądanych: W fazie 2/3 badań klinicznych z zastosowaniem dalbawancyny zidentyfikowano poniższe działania niepożądane. Działania niepożądane podano zgodnie z klasyfikacją układów i narządów oraz według częstości występowania. Kategorie częstości występowania zostały opisane zgodnie z następującymi normami: bardzo często (1/10), często (1/100 do <1/10), rzadkie (1/1000 do <1/100), bardzo rzadkie (1/10 000 do <1/1000).

| Klasyfikacja układów i narządów | Częste | Rzadkie | Bardzo rzadkie |
|---|---|---|---|
| **Zakażenia i zarażenia pasożytnicze** | | zakażenia grzybicze pochwy i sromu, zakażenia dróg moczowych, infekcje grzybicze, zapalenie okrężnicy wywołane *Clostridium difficile*, kandydoza jamy ustnej | |
| **Zaburzenia krwi i układu chłonnego** | | anemia, trombocytoza, eozynofilia, leukopenia, neutropenia | |
| **Zaburzenia układu immunologicznego** | | | reakcje anafilaktoidalne |
| **Zaburzenia metabolizmu i odżywiania** | | zmniejszony apetyt | |
| **Zaburzenia psychiczne** | ból głowy | bezsenność | |
| **Zaburzenia układu nerwowego** | | zaburzenia smaku, zawroty głowy | |
| **Zaburzenia naczyniowe** | | nagłe zaczerwienienie, zapalenie żył | |
| **Zaburzenia układu oddechowego, klatki piersiowej i śródpiersia** | | kaszel | skurcz oskrzeli |
| **Zaburzenia żołądka i jelit** | nudności, biegunka | zaparcie, ból brzucha, dyspepsja, uczucie dyskomfortu w jamie brzusznej | |
| **Zaburzenia skóry i tkanki podskórnej** | | świąd, pokrzywka | |
| **Zaburzenia układu rozrodczego i piersi** | | świąd sromu i pochwy | |
| **Zaburzenia ogólne i stany w miejscu podania** | | *reakcje związane z infuzją* | |
| **Badania** | | zwiększona aktywność dehydrogenazy mleczanowej we krwi, zwiększona aktywność aminotransferazy alaninowej, zwiększona aktywność aminotransferazy asparaginianowej, zwiększone stężenie kwasu moczowego we krwi, nieprawidłowe wyniki testu czynności wątroby, zwiększona aktywność aminotransferaz, zwiększona aktywność fosfatazy zasadowej we krwi, zwiększona liczba płytek krwi, zwiększona temperatura ciała, zwiększona aktywność enzymów wątrobowych, zwiększona aktywność gamma-glutamylotransferazy | |

Opis wybranych działań niepożądanych: Ototoksyczność związane z klasą leków: Ototoksyczność jest związana ze stosowaniem glikopeptydu (wankomycyny i teikoplaniny); u pacjentów otrzymujących w skojarzeniu lek ototoksyczny, taki jak aminoglikozyd, ryzyka ototoksyczności może być zwiększone. Zgłaszanie podejrzewanych działań niepożądanych: Po dopuszczeniu produktu leczniczego do obrotu istotne jest zgłaszanie podejrzewanych działań niepożądanych. Umożliwia to ciągłe monitorowanie stosunku korzyści do ryzyka stosowania produktu leczniczego. Osoby należące do fachowego personelu medycznego powinny zgłaszać wszelkie podejrzewane działania niepożądane za pośrednictwem krajowego systemu zgłaszania. **Podmiot odpowiedzialny:** Durata Therapeutics International B.V. Spaces Zuidas II, Barbara Strozzilaan 101, 1083 HN Amsterdam, The Netherlands. **Przedstawiciel podmiotu odpowiedzialnego: Angelini Pharma Polska Sp. z o.o.**, ul. Podleśna 83, 05-552 Łazy, Polska, tel. +48 227 028 200, fax +48 227 028 202. **Pozwolenie na dopuszczenie do obrotu:** EU/1/14/986/001. **Kategoria dostępności:** Rpw.

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# Xydalba®

dalbawancyna

Moc 1 dawki w ABSSSI



## PIERWSZY, PODAWANY W 30-MINUTOWYM WLEWIE, 1-DAWKOWY ANTYBIOTYK STOSOWANY W LECZENIU ABSSSI[1]

XYD/06/2017/A

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1. Charakterystyka Produktu Leczniczego Xydalba (dalbawancyna) z dnia 30.01.2017.