Intrathoracic vacuum therapy in patients with thoracic empyema

by

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Glossary of abbreviations

ANOVA	analyzed using analysis of variance
ATS	American Thoracic Society
BPF	Bronchopleural fistula
CT-guided	Computer tomography-guided
EMM	Estimated marginal means
ESBL	Extended-spectrum beta-lactamases
HIV	Human Immunodeficiency Virus
IASLC	International Association for the Study of Lung Cancer
LOS	Length of stay in hospital
Mini-VAC:	Minimally invasive vacuum-assisted closure
Mini-VAC-Instill	Minimally invasive vacuum-assisted closure with instillation
MRSA	Methicillin-resistant Staphylococcus aureus
NPWT	Negative-pressure wound therapy
NSCLC	Non-small-cell lung cancer
OWT	Open window thoracostomy
OWT-VAC	Open window thoracostomy with Vacuum-assisted closure
VAC	Vacuum-assisted closure
VRSA	Vancomycin-Resistant Staphylococcus aureus

Contents

1. *Introduction*

1.1. Contextualization of problem

Nowadays mainstream thoracic surgery has its main focus on lung cancer, while other topics, like procedures for inflammatory conditions are out of central scope of active research. As no new antibiotics have been developed since the 1980s and the patient's pool of potential candidates for pleural empyema is expanding, the question of optimising and further developing of the present protocols and techniques requires a closer look.

The number of therapy-resistant thoracic empyema cases (MRSA, VRSA, ESBL etc…) due to antibiotic abuse is on a sharp increase with a dark promise of the antibiotic apocalypse [1-2]. Extended surgeries and combined anticancer treatment modalities (neoadjuvant and adjuvant therapy) within and beyond the scope of thoracic surgery are contributing to the potential pool of postoperative empyemas [3]. The lung cancer procedures are performed in an ageing population: another cofactor for inflammatory complications, due to comorbidities [4]. In addition, pleural sepsis in immunocompromised patients (transplantation, HIV, etc.) has become a frequent phenomenon [5]. Nevertheless, migration into Europe is leading to renaissance of pulmonary tuberculosis, non-tuberculous mycobacteriosis and other complex inflammations, formerly thought to nearly extinct in the Old Continent [6]. Furthermore, classic methods of wound therapy in debilitated patient are relatively expensive, so that one cm^2 wound treatment costs more than thousand U.S. dollars [7]. Another aspect is the price of surgery, which can be as high as 150 USD/operational minute in theater.

Different types of pleural empyemas (chronic and recurrent empyema, sepsis, high risk patients with multiple co-morbidities or immunosuppression) are commanding a need to optimise existing treatment modalities and to look for new approaches to treat that complex phenomenon. Contemporaneously, the introduction of vacuum-assisted closure therapy (VAC therapy) in the general surgery provided new and

more importantly faster and safer treatment options for a range of sources of infection [8-9].

Therefore a project was initiated with a focus on the pleural empyema and ways of development of the established modern methods and application of VAC in the chest were explored. Five years of active research, development and clinical testing on pleural empyema is summarised on the following pages.

2. *Defined aims of the thesis*

2.1. Are there alternative modalities to standard Open Window Thoracostomy with equivalent success rates but less inconvenience and/or shorter treatment time?

2.2. Chest VAC is an in hospital method at the time being. What are the possibilities of continuation of the vacuum therapy in an outpatient setting?

2.3. In case of postresectional thoracic empyema what is the efficacy/applicability of intrapleural VAC when expandable lung as biological prosthesis is missing or diminished in volume/extent?

2.4. How to reduce interventional agressivity in thoracic empyema without compromising efficacy of VAC method?

2.5. What is the place of minimally invasive intrapleural VAC and how to develop further the method in complex situations caused by highly agressive bacteria and/or reduced immunity patients?

2.6. Which technique (OWT-VAC vs. Mini-VAC vs. Mini-VAC-Instill) is superior in the management of primary and postoperativ empyema in debilitated patients?

2.7. What are the limits of VAC therapy in the context of present paradigm of thoracic empyema and related intraparenchymal scenarios?

2.8. Is it possible to extent intrapleural VAC therapy applications to combined intraparenchymal /intrapleural - lung abscess cum pleural empyema scenarios - pathologies?

2.9. What are the indications summarized of intrathoracic VAC therapy up to day?

3. *State of the art*

3.1. Background

Reports of inflammatory diseases affecting the lung and thorax have been handed down from centuries past to the present day. They have long since fascinated doctors from all cultures and countries. The surgical treatment of these diseases still represents a challenge even today.
Pleural empyema is a condition in which pus collects in the pleural space with a subsequent inflammatory reaction in the parietal pleura, producing a characteristic morphological sequence of events. Even Galenus [10] described how an empyema that did not exit spontaneously outwards through the thoracic wall (empyema necessitates) can only be treated with an incision: "Ubi pus, ibi evacuae".

Primary thoracic empyema follows bacterial or viral lung inflammations. Majority of cases can be treated effectively by thoracocentesis or nether with single drainage of the empyema space. Pleural empyemas secondary to thoracic surgery and chronic empyemas are more difficult to treat. Pleural empyemas following thoracic surgical resection are usually caused by bronchopleural fistulas in the parenchyma or of the bronchial stump insufficiency. Post-pneumonectomy empyema is the most-feared form of the condition, since it is associated with a high degree of mortality [1].

Protracted treatment due to complications arising from acute empyema is leading to chronic empyema thoracis. In addition, poor general condition of the patient, pleural empyema on a background of multiple co-morbidities or immunosuppression can also result in chronification of empyema. Even today, chronic empyema remains a life-threatening condition due to the possibility of penetration into neighbouring organs, the metastatic transfer of bacteria and general toxic effects.

Therapeutic escalation ranges from thoracocentesis / thoracic drainage and thoracoscopic debridement to open decortications (Figure 1). Evacuation of the empyema to treat the local infection is always the primary goal in this context.

Thoracotomy is obiviously associated with markedly elevated postoperative morbidity (blood loss, persistent air leak following decortication, further thoracotomy for recurrent empyema) and risk of mortality in patients [11].

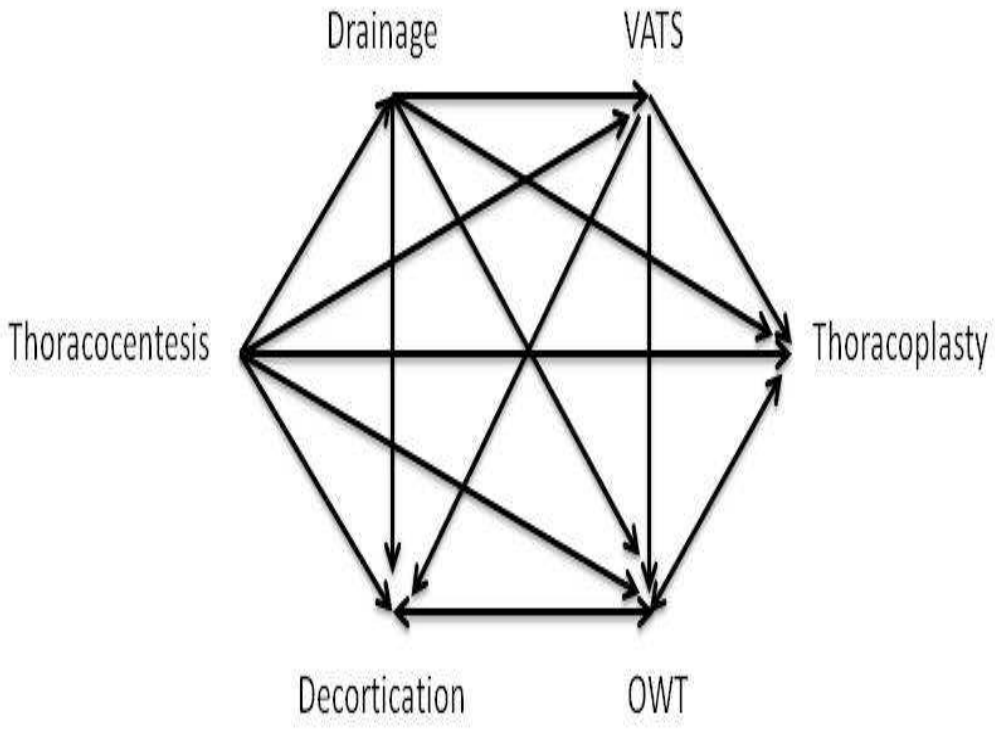

Figure1: Treatment modalities according to the therapeutic pathways: the empyema diamond (Source: Molnár TF, Benkő I: Management of primary empyema thoracis. 4th European Conference on General Thoracic Surgery, Cordoba, Spain, 1996, Abstract Book 059).

In complex cases, not rarely as an "ultimum refugium" an open window thoracostomy is often carried out with the partial resection of 2-3 ribs in order to control the acute situation (sepsis). This leads to a protracted period of recovery, however, and a marked limitation of the patient's quality of life. The thoracic window allows conservative treatment of the wound to be carried out using “abdominal” gauzes and changing them at regular intervals (Figure 2), In case of bronchial stump insufficiency; it can also serve as a means of sealing air leak. It can be applied either as a definite treatment with intent to cure, or a preliminary procedure prior to definite treatment or as a last resort procedure when others have failed. The goal is detoxication and a relatively stable disease [1].

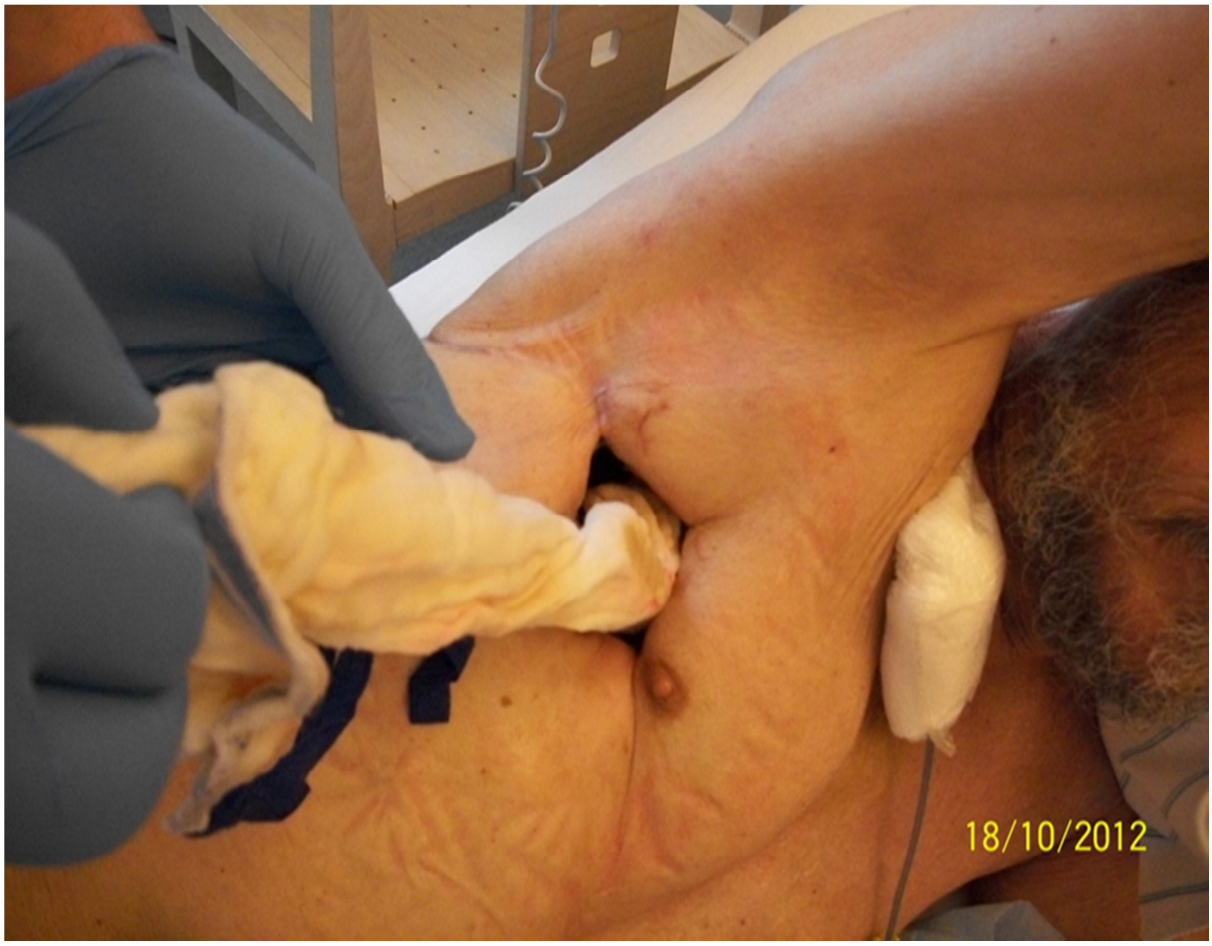

Figure 2: Open window thoracostomy, daily dressing change.

The intervals are varying, but not infrequently daily dressing changes are required in such cases. The infected pleural cavity can be closed by secondary intention if it is sterilized and the patient's condition allows major surgery (thoracoplasty ± space filling procedure).

3.2. Empyema stages and clinical applicability of classifications

Pleural empyema was first classified in 1962, when the American Thoracic Society (ATS) published a scheme which separated pleural empyema into three stages. It was based on its natural course regardless to its origin [12-13]. It consisted Stage I: Exudative phase, Stage II: Fibrinopurulent phase, Stage III: Organisation phase.

Stage III is the more important for us, as the formation of a fibrinous, inelastic membrane over the surface of both pleural layers results in trapped lung [12-14]. At the same time, a progressive negative intrapleural pressure develops secondary to thickening of the exudate. As a result of this, spontaneous clearance in form of outward (empyema necessitatis) or inward (bronchopleural fistula) perforations may develop [12].

After its publication, the ATS classification maintained its validity for a period of several decades. However with regard to the development from parapneumonic pleural effusion to pleural empyema, it exhibits clear gaps [15]. These were highlighted with the classification system devised by the pneumologist Light [15-16]. His nuanced complex classification allows precise staging, however due to its detailed structure, this classification narrows the applicability of treatment in everyday clinical settings [15]. Alongside the ATS classification [12], the simplified version developed by Muers enjoys considerable popularity in everyday clinical situations [13, 17]. This version classifies the condition into just three stages: uncomplicated parapneumonic pleural effusion, complicated parapneumonic pleural effusion and pleural empyema. In addition to the characteristics of the pleura and the punctate obtained, the classification also makes reference to the cytological, microbiological and biochemical parameters of the pleural punctate.

The stages have been classified in this review in accordance with the ATS classification [12] into the three morphological stages, representing the histological findings.

3.3. Side notes on history

3.3.1. Thoracic fenestration / Open Window Treatment

For debilitated patients with pleural empyema, open window thoracostomy is an old method to prevent/solve sepsis. The first publication to discuss thoracic fenestration by the London-based thoracic surgeon John Godlee appeared in 1886 [10, 18].

Eloesser published his thesis on the treatment of post-tuberculosis empyema in 1935 [19]. The concept, which still remains valid today, is executed via an inverted U incision with the simultaneous resection of 2 ribs and subsequent intra-thoracic rotation of the skin / subcutis / muscle / soft tissue flap, followed by fixation of the flap at the deepest point of the pleural angle or diaphragm. The inversion is intended to prevent the wound from healing too quickly and also acts as a matrix for intra-thoracic epithelialisation. The Eloesser approach allows daily cleaning of the cavity until it heals and subsequent primary closure through remobilisation of the flap with direct closure of the thoracotomy with or without the instillation of an antibiotic solution into the cavity [20].

In 1963, Clagett published his technique for treating pleural empyema following pneumonectomy with bronchial stump insufficiency [21]. The concept includes the initial opening of the thoracic cavity with resection of 1 or 2 ribs, debridement of the pleural cavity, closure of the insufficient bronchial stump with direct suturing, subsequent inversion of the incised skin. Sterilisation was performed by the infected cavity with daily packaging of the cavity with swabs soaked in Neomycin over a period of up to 3 months. The cavity is then closed after being filled with an antibiotic solution. The success rate was 88% in the initial publication [21]. The failure rate exclusively involved cases with recurrences of the bronchial stump insufficiency.

One of the most important modifications to the Clagett procedure to prevent further bronchial stump insufficiency was the use of vascularly pedunculated muscle flaps (serratus anterior muscle, latissimus dorsi muscle, intercostalis externus and internus muscles) to cover the reconstructed bronchial stump in combination with the classic Clagett procedure [22-23]. The problem with the (modified) Clagett procedure is the long period of inpatient stay, which ranges from several weeks to months.

The Zürich-based working group led by Walter Weder modified the Clagett method by performing radical open surgical debridement of the pleural cavity with subsequent packing to sterilise the cavity (gauzes carrying 20:1 polyvidone-iodine solution) in cases of post-pneumonectomy pleural empyema with and without bronchial stump insufficiency [24-25]. An existing bronchial stump insufficiency was closed if necessary with an omentum majus flap, as this was felt to offer the best potential for

healing [26]. The thoracic cavity was temporarily closed and the procedure repeated every 48 hours for a total of 3 times. Following the 3rd repeat, the cavity is filled with a solution comprising an antibiotic combination of an aminoglycoside, ampicillin / clavulanic acid and vancomycin and then permanently closed. The success rate was 100% with a reduction in inpatient duration to a median of 17 days [25]. The effectiveness of this method was confirmed in a bi-national study which reported a success rate of 97.6% and a median hospitalisation period of 18 days [25].

3.3.2. Surgical treatment of pulmonary abscess

3.3.2.a. Drainage of tuberculosis cavities by aspiration (Monaldi Method)

Empyema thoracis can be further complicated and accompanied by lung abscess. This two-in-one scenario is an extrem challenge. Empyema thoracis is characterised by a preformed layer as a membrane. Abscess of the lung is characterized by a pseudomembrane, with poorly defined borders. As it is sitting deeply within the parenchyma, a simple chest tube is out of the question as it should go through a „relatively" healthy lung tissue. There are two approaches to solve a lung abscess – inside-out or outside in. Transbronchial (per vias naturales) clearance, via (rigid) bronchoscope – requires a draining secondary/tertiary bronchus (Friedel-drainage). Than the patient will „cough out" the contain of abscess. The other option is to follow the Monaldi's drainage [27] (Italy, 1936, originally for tuberculotic abscesses) – when a layer of healthy tissue had to penetrate to let the cavity contain to come out. A circumscribed (provoked) empyema thoracis allowed a direct access to the involved parenchyma if the abscess sat close enough to the viszeral surface. Following that a deroofing opened up the way out: abscess > pleural space > chest-wall-skin.

3.3.2.b. Lung abscess resection

The tasks of surgery include the prevention of sepsis and managing complications. Complicated lung abscesses are associated with high mortality rates of up to 23% [28]. Standard surgical treatment includes debridement of the abscess or even

pulmonary wedge/anatomical resection. It is often combined with prolonged hospitalization [28].

Despite significant advances in the treatment of thoracic infections, complex (e.g., failed primary treatment) lung abscess remains a problem in modern thoracic surgery. Large abscesses and anaerobic bacteria are associated with worse outcome [29]. The prognosis is poor in elderly, debilitated, malnourished, and immunocompromised patients. If the patient is medically unstable, a quick evacuation of pus can be performed by thoracocentesis via a chest tube.

3.3.2.c. Cavernostomy for pulmonary Aspergillosis

Aspergillus infection is a quite recent thoracic surgical challenge. The most effective treatment for a complex pulmonary aspergilloma is resection of the diseased lung. However, this is contraindicated for patients with poor pulmonary function or poor general condition. Immediate infection control via cavernostomy is the treatment of choice to prevent deterioration [30].

Either fenestration with rib resection or tube fenestration are performed, each of which has limitations. Fenestration with rib resection is highly invasive, whereas tube fenestration often provides insufficient drainage. The long-term survival of patients who underwent cavernostomy is comparable to those patients who had lobectomy or segmentectomy [31]. Regnard et al. showed, in some cases, the cavernostomy has been successfully closed by a muscle flap, enhancing further this surgical option [31].

4. *Theoretical consideration of VAC therapy*

Pressure is an important element of life on Earth as the subatmospheric intrapleural environment proves it. Pressure has a direct relevance to wound healing also [32-33]. Pressure is measured in fluids (liquids and gases) and its actual force is defined as the force applied divided by the area to which it is applied (Figure 3).

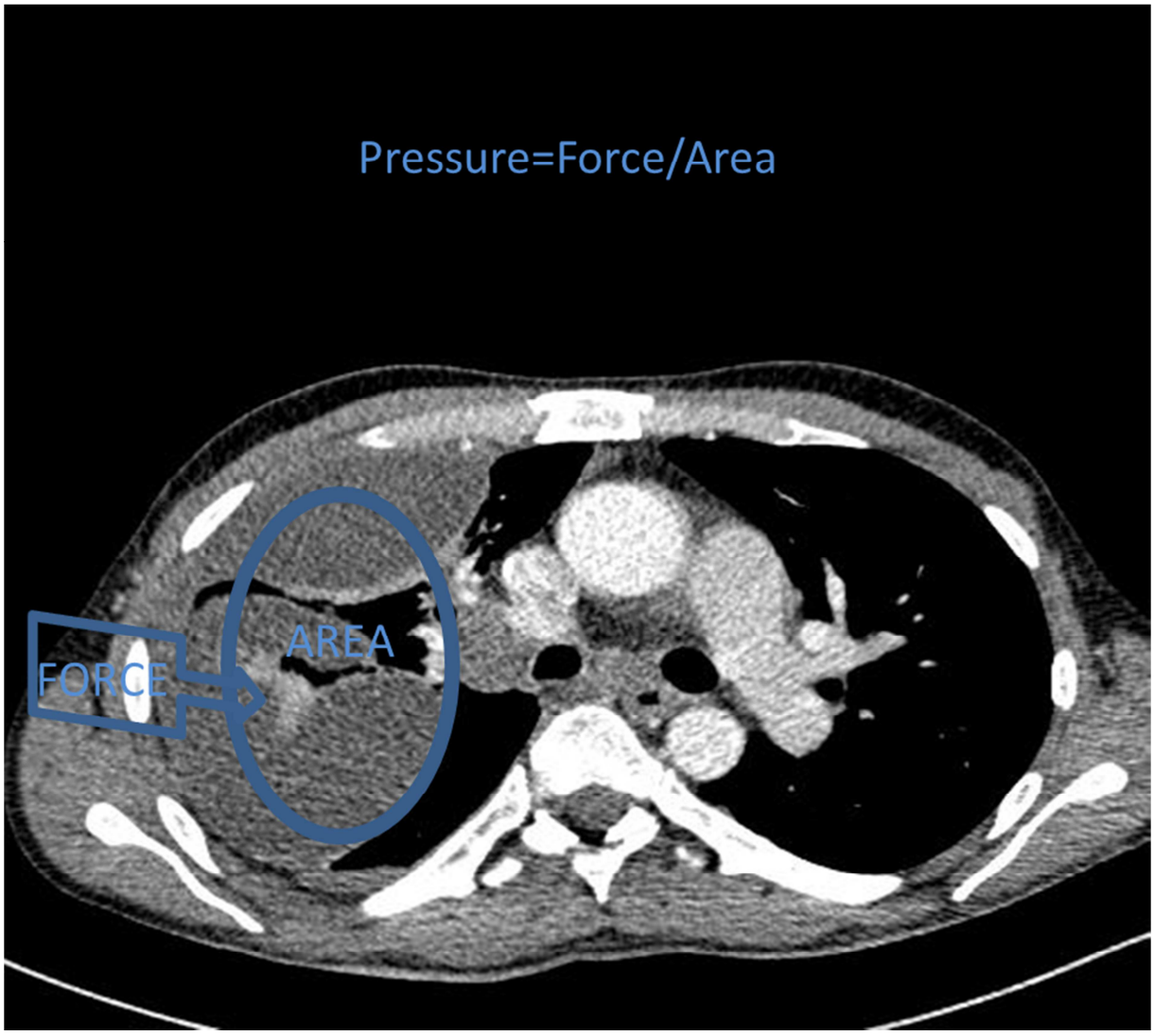

Figure 3: Pressure = Force / Area

On Earth at sea level, we are subjected to atmospheric pressure, about 101325 Pa on our bodies equals 760 mm of mercury (0 °C).

Mathematically for an ideal gas, the relationships between pressure, volume, and temperature are defined as:

$$P \times V = n \times R \times T$$

Where: P = pressure, V= volume, n = number of moles of gas, R = Universal gas constant, T = temperature in degrees Kelvin

Volume and temperature are always positive numbers; therefore, pressure is always going to be a positive number. Many times, pressure is measured as the difference between the pressure of interest and a reference pressure (gauge pressure, in reference to atmospheric pressure). The pressure is negative when it is referred to suction resulting in vacuum.

Many authors prefer the terms “subatmospheric pressure wound therapy” or “microdeformational wound therapy” to describe these types of devices. In essence, suction is applied to a wound through an interface material that is covered with a nearly nonpermeable covering. This facilitates the removal of fluids and also pulls the wound edges together [34-35].

Suction is applied to create a pressure up to 125 mm Hg below ambient pressure (atmospheric pressure). It is not the absolute pressure that facilitates wound healing. Lower absolute pressure is felt in high-altitude locations, or in the cabin of a pressurized jet. Wound healing in either of these environments is not faster than wound healing at sea level. Therefore, it must be the pressure differential that leads to the changes in wound healing [34-35]. VAC/NPWT therapy has primary and secondary effects [34].

4.1. Primary effects

(1) Macrodeformation: The open-pore foam draws the wound edges together, depending on the mobility of tissues surrounding the wound. In obese patients with an open abdominal wound, VAC will bring the edges close to approximation. In contrast, for a large scalp wound, there will be little deformation of the surrounding tissues [35].

(2) Microdeformation: It is supposed that deformation of the wound surface at a microscopic level stretches cells, triggers the matrix facilitating division and proliferation [36] leading to a mechanosensitive cellular response.

(3) Fluid removal: The surrounding wound tissue are always oedematous. VAC has the capacity to remove large amounts of fluid from the extracellular space [37].

(4) Environmental control of the wound: VAC provides an insulated, warm and moist environment [38].

4.2. Secondary effects

(1) Granulation tissue formation: Robust granulation tissue response occurs as a result of VAC application. There are likely several contributing primary mechanisms including microdeformation, which induces localised hypoxia near the wound surface that upregulates the HIF-1alpha-VEGF pathway [39].

(2) Cell proliferation: At least three of the primary mechanisms are likely to contribute to proliferation, including microdeformation, fluid removal and maintenance of a warm and moist wound environment [35, 37].

(3) Modulation of inflammation: Inflammation is a critical response to injury, and we are just beginning to learn how this is modulated by VAC. Granulation tissue response in mast cell-deficient mice has been shown to be muted, suggesting that mast cells are critical for VAC success [40].

(4) Change in neuropeptides: Investigators have previously shown in a mouse model that NPWT upregulates neurotransmitters [41].

(5) Change in causative organism number: Various studies have shown both increased and decreased bacterial levels following the use of VAC [35-38, 42]

The effect of subatmospheric pressure therapy on blood flow has also been evaluated in vivo. Laser Doppler needle probes measured blood flow in a porcine wound model treated with varying levels of subatmospheric pressure therapy (Figure 4). A maximum increase in blood flow was found at – 125 mm Hg after testing a range of – 25 mm Hg to – 4 00 mm Hg. This increase in blood flow leads to improved

oxygenation and nutrient delivery to the wound bed. These results correlate with a 63.3% faster formation of granulation tissue under - 125 mm Hg continuous therapy versus wet-to-dry saline dressings. [32].

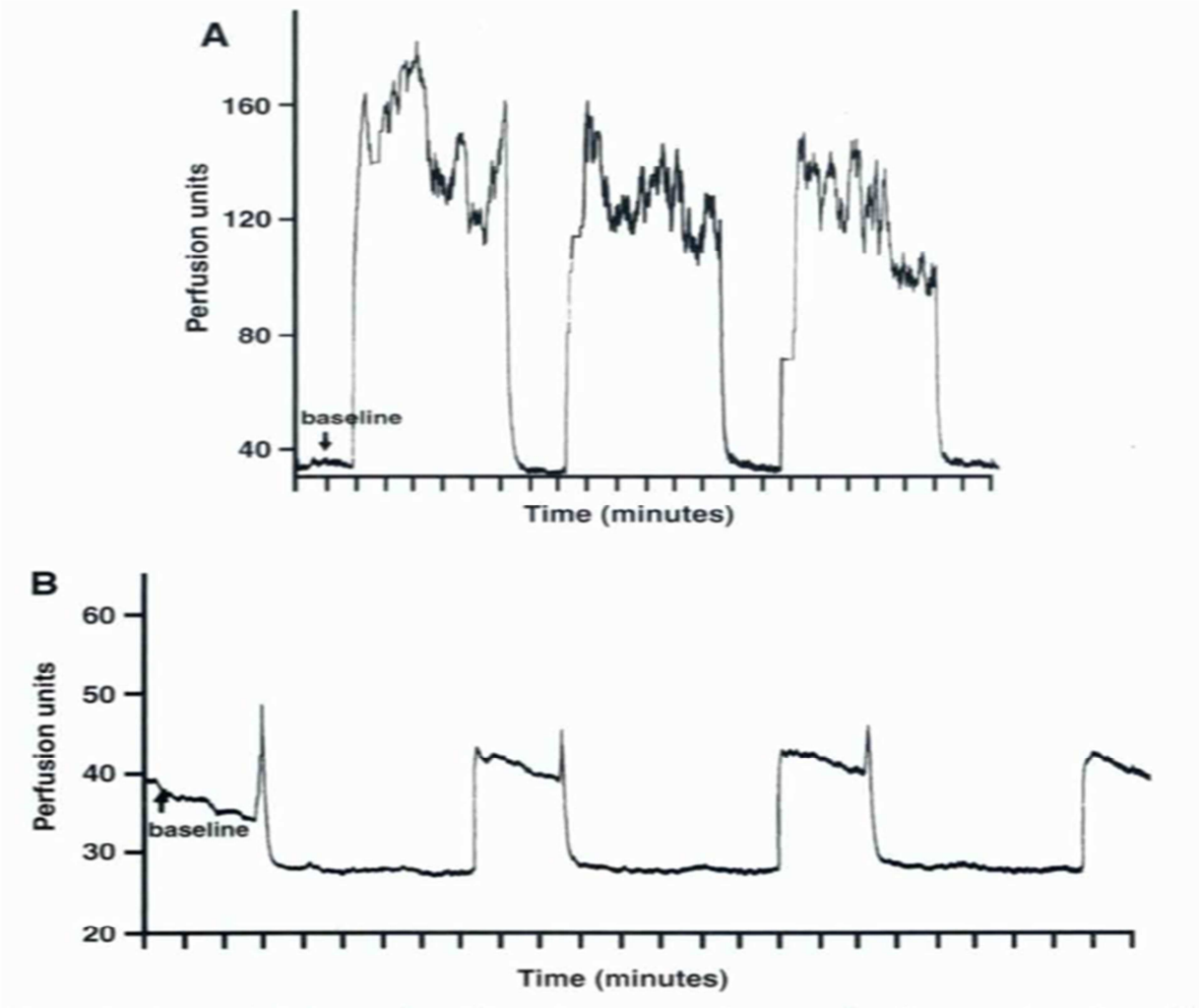

Figure 4:

A) Recording from laser Doppler needle flow probe placed into subcutaneous tissue at edge of wound. B) Recording from laser Doppler needle flow probe placed into subcutaneous tissue at edge of wound. From Morykwas MJ, Argenta LC, Shelton-Brown EI, et al. Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation. Ann Plast Surg 1997;36(6):553-62.

The vacuum treatment of superficial wounds was initially introduced in burns surgery [32] and then gradually extended from the treatment of superficial wounds through to complex treatment following cardiac surgery procedures, including sternal resection following osteomyelitis secondary to sternotomy [43].

Vacuum therapy offers a closed wound care system, from acute septic cases to chronically persistent wounds. An electronically controllable pump provides a controlled, restricted negative pressure using a sponge inserted into the wound. VAC therapy allows wound secretions to drain, reducing the amount of wound oedema and also encouraging perfusion of the blood in the wound. Heterogeneity of the pressure distribution allows interstitial fluid to be transported away more effectively. This mechanism could explain the anti-oedematous function of vacuum therapy, which can then lead secondarily to improved perfusion of the tissue [44]. Granulation tissue forms and moist wound treatment is possible without any build-up of wound exudate. The vacuum can be continuous or intermittent.

Introduction of vacuum-assisted closure therapy (VAC therapy) in general surgery provided faster treatment options for a range of sources and forms of infection [9, 45]. Following the initial case reports in thoracic surgery on the treatment of pleural empyemas [46-47], the indication for this treatment has been increasingly widened over recent years. There are now initial reports on the successful treatment of pleural empyemas following pneumonectomy with and without bronchial stump insufficiency with and without treatment of the pleural cavity via a temporary thoracic window [48-49]. The common argument in all publications is an improvement in patient comfort: an "open" procedure is being carried out. However it is a "closed" system. For patients, this method offers considerably more benefits from hygiene and social life perspective since the wound is cleaned quicker. It offers a significant reduction in bacteria due to the immediate aspiration of exudate without danger of additional bacterial colonisation. The wound is easier to care for (fewer dressing changes). Odour neutrality also offers an increased quality of life for the patient [50]. However, unfortunately no randomised studies are so far available into vacuum sealing for pleural empyemas to prove these hypotheses [49].

The reviews of randomised studies for vacuum therapy in other applications then chest are currently unable to definitively confirm the additional benefits of vacuum therapy [8, 49]. Conventional wound treatment concepts in comparison with vacuum methods (end point: complete wound closure) are not definied [8, 45, 49]. For the end point of "time until wound closure", most reports have been of effects in favour of the NPWT group [49]. Measurement and analysis methods vary greatly, between the

studies, as the non-blind documentation of this end point representing a particular problem. Most studies also failed to investigate whether successfully healed wounds actually remain closed in the long term. The interpretation of the results so far does not permit any definitive conclusions regarding to the advantage of one treatment over another [51-53].

Objective of the present project was - as objective as possible - a comparison and outcome analysis of vacuum therapy versus classical methods performed in one center followed by one standard operating procedure.

5. *VAC treatment modalities*

Three main modalities i.e. OWT-VAC, MINI-VAC and MINI-VAC-Instill were investigated separately in order to evaluate the the effectiveness of intrathoracic negative pressure therapy for empyema thoracis and to compare the short-term and long-term outcomes of three different intrapleural vacuum-assisted closure techniques.
Internationally pioneering studies and their observations cover the topic and multi-peer reviewed reported results [54-56] are forming the pillars of this clinically focused project.

5.1. OWT-VAC Study

OWT followed by VAC was initiated by us in 2009 [54]. A new policy was established and its results reviewed as follows. There was a focus on VAC in case of BPF in eight risk patients.

5.1.1. Patients and Methods

Study sample

There were eight patients with multimorbidity (Karnofsky index < 50%), investigated retrospective and treated for secondary pleural empyema (i.e. postoperative or recurrent postpneumonic) between October 2009 and July 2010. Patients who received VAC therapy for mediastinitis after cardiac surgery or for chest wall abscesses not involving the pleural space were excluded.

Patient demographics

All patients were men with a mean age of 66.1 years and a range of 53 to 76 years. Patient demographics and lung pathologies are summarised in Table 1. Four patients had previous lung cancer and two of them received induction chemotherapy, specifically radiochemotherapy. The resection of the tumour included one

pneumonectomy, two lobectomies and one lower bilobectomy. Three R0 and one R1 resection were confirmed. The patient with R1 resection received subsequent completion pneumectomy because of BPF. Other postoperative empyemas resulted after chest wall reconstruction for rib resection (fracture) and lung volume reduction (emphysema). Two decortications were performed. Five patients presented an early/acute (≤ 30 days after primary thoracotomy, with a mean of 24.7 days) and three patients a late/chronic pleural empyema (> 30 days, with a mean of 68 days). Only two patients (25%) had BPF. In five of eight patients, an initial intervention for treatment of the detected empyema was performed (Table 1). Independent from the time of empyema, Staphylococcus, Streptococcus, and anaerobic species were the most frequently isolated organisms. Aspergillus fumigatus was found in two patients.

Table 1: Demographics of OWT-VAC patients

Variable	P1	P2	P3	P4	P5	P6	P7	P8
Age	66♂	71♂	67♂	76♂	74♂	69♂	53♂	53♂
Original Karnofsky Index <50%	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Diagnosis	NSCLC Stage IIA	Inveterated rib fracture	NSCLC Stage yIII A	Atelectasis, pleural effusion	Postpneumonic empyema	Emphysema	NSCLC Stage IIIA	NSCLC Stage yIIB
Neoadjuvant Therapy	No	No	Radiochemo.	No	No	No	No	Chemo.
Primary Operation	Lobectomy R0	Chest wall stabilisation	Lobectomy R0	Decort.	Decort. (thoracoscopic)	Volume Reduction	Bilobectomy R1	Pneumectomy R0
Pathophys. of Empyema	Postop.	Postop.	Postop.	Postop.	Postop. (Recurrent postpneumonic)	Postop.	Postop.	Postop.
Onset	Acute	Chronic	Acute	Chronic	Chronic	Acute	Acute	Acute
BPF	Yes	No	No	No	No	No	Yes	No
Number of Interventions	2	1	1	0	0	1	1	0
Intervention before OWT-VAC	Comp. Pneu. Débridement	Débridement	Chest Tube	-	-	Chest Tube	Comp. Pneu.	-
Microbiological findings	Strep. Staph.	Staph.	Staph.	Staph. Pseudo.	Strep.	Enterobac. Asperg.	Staph. Asperg.	Staph.

P: Patient, NSCLC: Non-small cell lung cancer, Decort.: Decortication, Stage: IASLC, Enterobac.: Enterobacter, Strep.: Streptococcus, Staph.: Staphylococcus, Asperg.: Aspergillosis, Acute Empyema: <30 days, Comp. Pneu.: Completion pneumectomy, pathophys.: Pathophysiology

5.1.2. Surgical procedure (OWT and VAC therapy)

The operation for OWT and VAC included the resection of 2-4 ribs, pus evacuation, debridement, flushing the cavity with Ringer solution and 10% Betaisodona (Povidon-Iod, Mundipharma, Limburg, Germany) solution. Suturing the skin flaps on the margins of the OWT constituted the thoracostoma. The VAC sponges (black GranuFoam Standard Dressings, 400 - 600 microns, KCI Medical, Wiesbaden, Germany) were inserted in the residual pleural cavity through the thoracostoma to fill the pleural space. The sponges covered the leakage directly; no interface membranes were applied for the BPF or the remaining lung. To avoid direct contact of the VAC device with the mediastinum, the area was covered with Mepitel (Mölnlycke Health Care, Erkrath-Unterfeldhaus, Germany). Mobile vacuum system ActiV.A.C. (KCI Medical, Wiesbaden, Germany) was applied. Suction was set to -100 mmHg from the start (then increasing until maximum suction -125 mmHg), but in two patients with pneumonectomy, the initial suction was only -75 mmHg. The sponges were changed once or twice a week, depending on the incorporation of the granulation tissue into the sponges. Only a small amount of debridement was required at each sponge change.

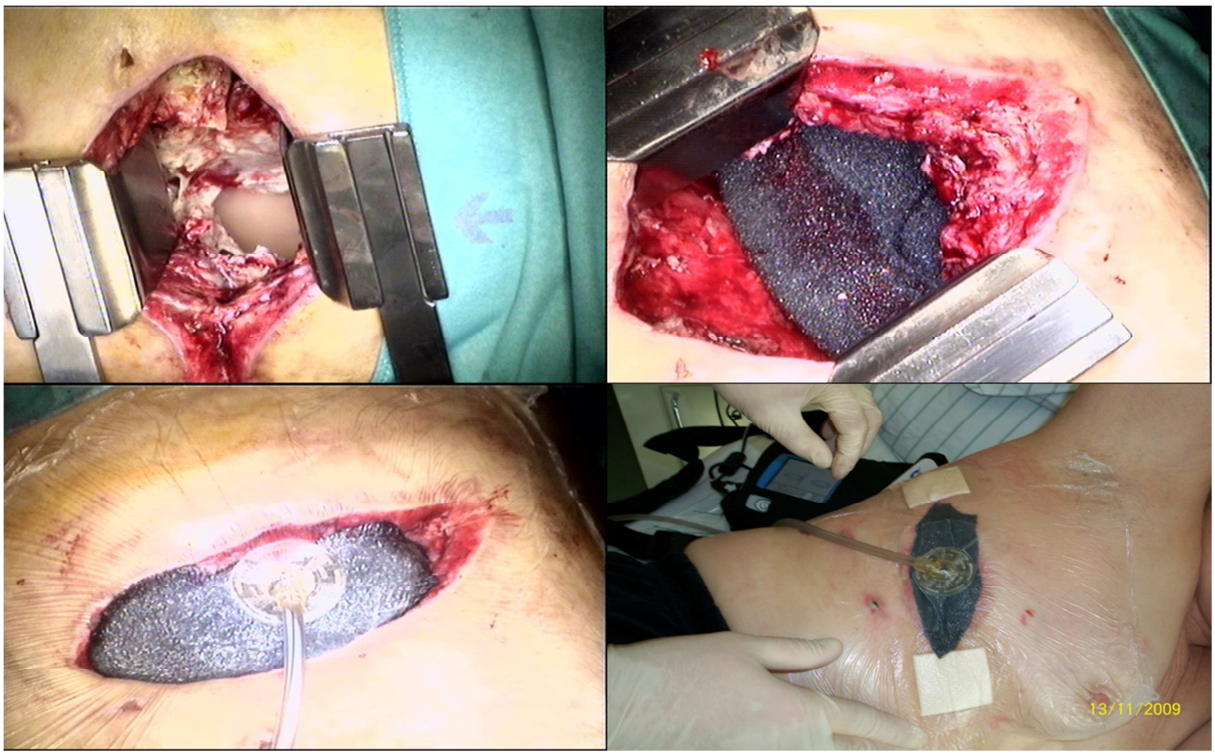

Figure 5: OWT-VAC procedure: thoracostomy, debridement and decortication, insertion of the vacuum foams and mobile suction.

5.1.3. Results of OWT-VAC

Indications and time of OWT and VAC

The indication for OWT and VAC intervention was acute sepsis, failed primary surgical intervention (e.g., tube insertion) or complications of primary interventions. The mean time between primary thoracotomy and OWT was 52 days (range 21 days to 126 days). In five patients, either chest tube drainage or rethoracotomy with completion pneumectomy/debridement initiated the empyema treatment (Table 2). Four patients underwent one initial intervention before the fenestration and vacuum closure. One patient had two previous interventions. In two patients BPF was detected, directly closed by stitches and covered by a pericardial fat flap during the first intervention. All five patients received the OWT and VAC secondarily because of failed initial empyema treatment. A priori creation of OWT with VAC therapy was performed in three patients. The mean time between the first intervention and OWT with VAC therapy was 18.4 days for directly treated patients. 33.5 days elapsed in average for patients with delayed OWT with VAC therapy.

Course of OWT-VAC therapy

Local control of the infection and control of sepsis was satisfactory in seven of the eight patients treated by OWT and VAC therapy. The patients tolerated a suction of 75-125 mm Hg. No arrhythmia or haemodynamic complications were detected due to the traction on the mediastinum during attempts to increase the suction. Membranes for the protection of the lung parenchyma were not applied. The suction did not create any air leak or bleeding from the lung or the mediastinal structures. At the time of OWT and VAC installation, three patients were in acute respiratory insufficiency with mechanical ventilation. One patient was resuscitated. After implementing VAC therapy, two patients could be weaned from ventillatory support after one and five days. In patients with residual lung tissue, VAC therapy allowed improved re-expansion of the residual lung (Figure 6).

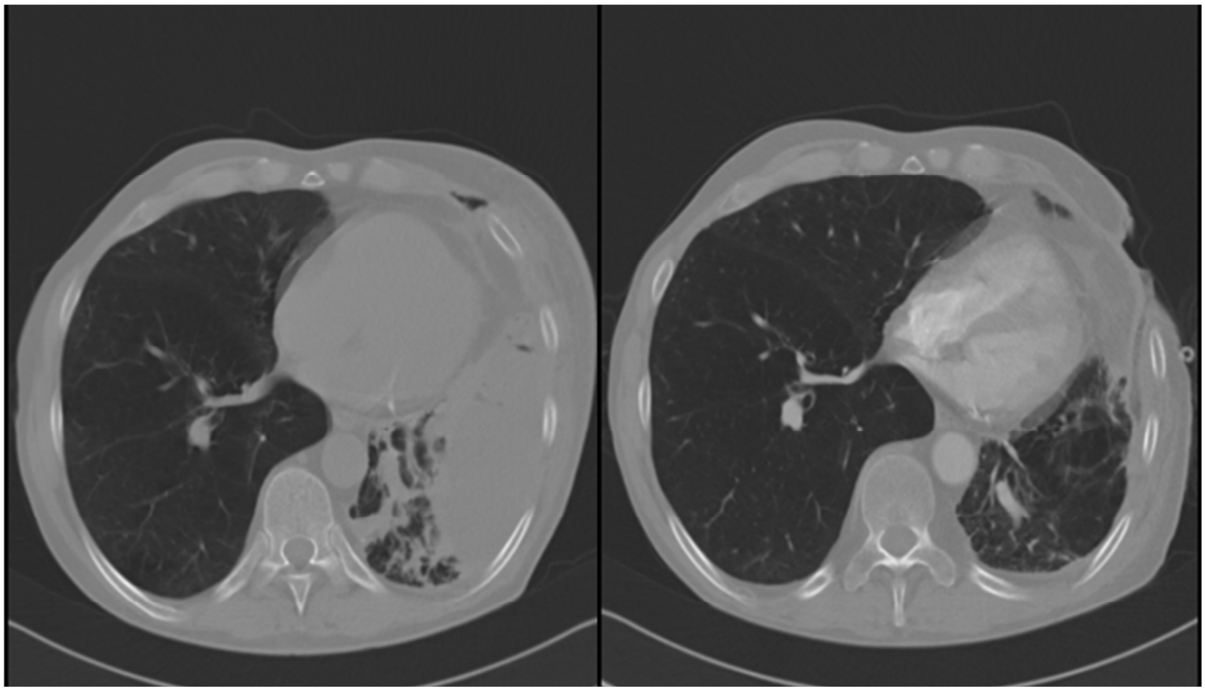

Figure 6: Radiologic demonstration that intrapleural VAC could help expand dystelectatic lung; on the left side is the CT before VAC and on right side is the CT after VAC therapy.

In both patients with BPF, these fistulas persisted following the first intervention. At this time, the recurrent bronchial stump insufficiency were (BSI) one millimetre and eight millimetres, and closing was not possible in either case. Both patients with BSI underwent successful local treatment of pleural empyema with suction. The smaller bronchus stump fistula closed spontaneous from VAC therapy, but the larger remained open.

In the beginning of the VAC therapy, dressing changes were performed under anaesthesia in the operating theatre, with a mean rate of 2.1 changes and a range of 0 to 5 changes. Additional changes were set individually and performed without analgesic two or three times a week. Antibiotic therapy was stopped when the microbiological culture did not show any further pathogenic bacteria colonisation (mean antibiotic therapy: 16.3 days).

Table 2: OWT-VAC and outcomes

Variable	P1	P2	P3	P4	P5	P6	P7	P8
Immediate / delayed Creation of OWT	Delayed	Delayed	Delayed	Immediate	Immediate	Delayed	Delayed	Immediate
Number of Interventions before OWT and VAC	2	1	1	0	0	1	1	0
Intervention	Compl. Pneumectomy/Débridement	Débridement	Chest Tube	-	-	Chest Tube	Compl. Pneumectomy	-
Indication of OWT+VAC	Sepsis	Bleeding Fistula	Failed Th.	Osteomyelitis	Fistula	Failed Th.	Sepsis	Muscle necrosis
P.o. mechanical ventilation after VAC	Yes	No	No	No	No	Yes	Yes	No
Number of VAC Changes in OR	4	2	2	1	0	5	3	0
Max. Suction in mm Hg	- 75	- 125	- 125	- 125	- 100	- 100	- 75	- 125
Hospitalization in days after VAC	22	45	17	15	14	38	47 (exitus)	8
Antibiotic Therapy, in days	10	12	7	6	7	19	47	6
Clinical outpatient VAC	No	No	No	Yes	Yes	No	-	Yes
Outcome	Healed	Healed	Healed	Healed	Healed	Healed	Died of Sepsis	Healed
Closing planned	Yes	Yes	Yes	Yes	Yes	Yes	-	Yes
Chest wall closed	No*	No*	Yes	Yes	Yes	Yes	-	Yes
OWT Duration, in days	not closed	not closed	51	39	31	164	-	59

P: Patient number, P.o.: postoperative, Max.: maximum, OR.: Operation room, Th. Failed primary intervention/operation *: closing was planned, but patient rejected it.

Outcomes of OWT-VAC

Seven of the eight patients (87.7%) were successfully treated by OWT and VAC therapy. One patient died in the late postoperative period (day 47 p.o.) of fulminant aspergillum sepsis-related multiorgan failure. He had persistent eight millimetres BPF, the thoracic cavity was sterile during VAC treatment and his death was due to other factors. The success of VAC therapy was defined by discharging the patients with a Karnofsky Index of 70% and above and with a steril pleural cavity. In most cases the dimension of the pleural cavity was also decreased by OWT and VAC therapy. The mean hospital stay after OWT and VAC installation was 22.7 days. Four patients left hospital without VAC, and the cavity was filled with dry dressing material. Three patients were transferred with VAC to the outpatient service. Despite ambulant VAC therapy, these patients had a good quality of life.

Following a mean time of three months (97.5 ± 66.5 days), the chest wall was closed in five patients. Muscle transposition was performed in three patients (M. pectoralis N = 2, M. serratus anterior N = 1). In two patients, the secondary closure was performed without thoracoplasty because of maximal contraction of the pleural cavity. Two patients subsequently rejected the closure of the OWT, the last follow-up (after 15 respectively 18 months) did not show sign of recurrent infection. After follow-up at an average of 7.7 months (range of 4 to 12 months), neither pleural empyema nor BPF recurred in any of the seven surviving patients. All of these patients reported a very good quality of life in an outpatient interview.

5.1.4. Comment to OWT-VAC therapy

Timing of OWT-VAC

In one VAC group reported by Palmen and colleagues [9], the OWT was delayed 58 ± 119 days after the diagnosis of the empyema. Once treatment commenced, the total duration of OWT with VAC therapy was 31 ± 19 days. In the present series, for comparison, patients with delayed OWT and VAC therapy left our hospital after 31 ± 14 days and one patient died. In patients with initial fenestration, however, the hospital stay was only 11.5 ± 3.5 days. This finding was consistent with Massera and

colleagues [57], who concluded that immediate creation of OWT is a significant predictor of successful thoracostomy closure. My observation support this opinion and extended early OWT installation to combined VAC therapy. OWT and VAC therapy should be considered soon as possible, especially for postoperative or chronic pleural empyema and in patients with increased risk for impaired wound healing (e.g., diabetes, obesity, steroids).

VAC in the presence of BPF

The presence of BPF or remaining lung tissue is not a contraindication for VAC therapy. Groetzner and colleagues [58], as well as Palmen and colleagues [9], defined patients with BPF as not qualified for VAC therapy. This recommendation led to Aru and colleagues [59] closing all of the BPF before application of the VAC system. The closure of a BPF is the mein precondition of empyema treatment. However, the closure is not always possible. Two BPF patients were successfully treated by VAC. In one patient with a one mm fistula, the BPF was sufficiently closed after VAC therapy. The other BPF (8 mm diameter) was resisted to VAC, but it did not exclude the treatment. Future studies should investigate the diameter of BPF that can be closed by negative pressure in VAC therapy.

Re-expansion of the remaining lung tissue

VAC therapy seems to have a beneficial effect on the re-expansion of the remaining lung in patients (Figure 3.). Two patients with respiratory insufficiency were quickly weaned off their respirators after VAC therapy.

Suction force

Similar to other reports [58-59], we applied a maximum suction of -125 mmHg directly to the pulmonary tissue using the V.A.C. GranuFoams. Starting with a lower suction (-75 mmHg) was useful in patients with prior pneumonectomy. Membranes to protect lung tissue protection were not applied neither needed. No major complications - like vagus excitement and arrhythmia, bleeding, mediastinal shift - related to vacuum-assisted management were observed.

Foam changes

Patients underwent sponge changes in the operating theatre under general anaesthesia every second to third day. The frequency and the location of intrathoracic VAC changes in patients with OWT vary, as this part of the surgical treatment is not defined. Palmen et al. [9] changed the system in the surgical ward without anaesthesia every third to fifth day, or more often in cases of purulent secretion or increased infection. However, Aru and colleagues [59] performed all sponge changes under general anaesthesia. For comparison, our patients underwent two debridements and VAC changes in the operation room, and additional changes were performed every 3rd to 5th day in the ward.

Antibiotics

In most cases, VAC therapy resulted in the rapid eradication of local infection. We therefore withdrew antibiotics when there were no signs of sepsis and the thoracic cavity became sterile (mean time of 16.3 days). However, the role of simultaneous antibiotics flushing (e.g., V.A.C. Instill) has not yet been investigated.

VAC in the outpatient setting

After treatment of sepsis and local control of the empyema, often with reduction of the pleural cavity, patients could be discharged to an outpatient service with initial daily wound care by specialized nurse technicians. It was occasionally useful to continue the VAC therapy in this ambulant sector with the aim of further reduction of the pleural cavity (in the present study, n = 3). Thoracic surgeons should perform this outpatient treatment weekly. In follow-up visits, the indication for closure of the OWT should be periodically evaluated.

Secondary wound closure

The OWT was closed after a mean time of three months, but two patients rejected this procedure. For comparison, Matzi and colleagues [60] performed closure of the thoracic cavity after VAC therapy in all cases between the 9th and 48th day (mean of

22 days). Groetzner and colleagues [58] used the VAC system as a bridge to reconstructive surgery and removed it after a mean of 64 +/- 45 days (range of 7 to 134 days). These patients underwent direct surgical wound closure, and complete healing without recurrence was achieved in 11/13 (85%) patients. Data from the literature show that the interval between installation and closure of the OWT is considerable longer in patients without additional VAC therapy [9, 61]. The average duration of OWT without VAC therapy at the Maastricht University Medical Centre was 933 ± 1422 days [9]. Maruyama and colleagues reported an OWT interval from 128 +/- 32.1 to 365.8 +/- 201 days, depending on indication [61]. In our patients with VAC therapy the chest wall was closed after a mean time of three months (97.5 ± 66.5 days). In the non-VAC group of Palmen and colleagues [9] six of the eight patients could be discharged home. In only two of them the OWT was closed by muscular flap. Four patients died during follow-up because of OWT-related complications (massive bleeding n=1, recurrent infections of the thoracic cavity n=3). The rate of successful empyema treatment and closure of OWT by reconstructive surgery is in my study as well as in other studies with VAC therapy [58, 60] substantial higher in correlation to groups with only OWT treatment. The closure of the OWT depends on the patient's individual situation (e.g., general condition of the patient, planned rehabilitation). As a final step, the closure of the chest guarantees full mobilisation and a good quality of life, with only a very low risk of recurrent infections.

5.1.5. Conclusion to OWT-VAC therapy

Patients with complicated empyema were successfully treated with OWT and VAC therapy, so the use of this procedure should be considered early. The most important advantages of the OWT with VAC were fast-tract treatment of sepsis and local control of the pleural cavity. Suction therapy could also improve pulmonary function (re-expansion). The presence of bronchial stump fistulas or residual lung tissue is not a contraindication for vacuum-assisted closure. Furthermore, the length of hospitalization seems to be shortened, based on comparasion with historical data and common experience.

Immediate OWT and VAC-therapy installation is advantageous. Outpatient treatment with VAC-therapy is feasible.

5.2. Mini-VAC Study

Until 2011 more and more reports [62] have demonstrated the advantages of VAC therapy in patients with Stage II and III empyema thoracis. However the initiation of this approach and the procedure used to change the VAC sponge require an OWT, with resection of the ribs and a secondary surgical procedure for closure. Having obtained experience and positive tests the feasibility of the minimally invasive insertion of the VAC system without OWT were proven [48]. A consecutive case series project of pleural empyema managed by Mini-VAC therapy without classical OWT was performed [55].

5.2.1. Patients and methods

Study sample

Six consecutive patients with multimorbidity (Karnofsky index ≤50%) treated for a primary or secondary pleural empyema between January 2011 and February 2012.

Patient demographics

The patient series consisted of 5 men and 1 woman with a mean age of 54.3 (range 41–72 years). Patient demographics and lung pathologies are summarized in Table 3. One patient presented with an early toxic pleural empyema (≤30 days), and two presented with very late/chronic postoperative pleural empyema (328 and 602 days) after primary thoracotomy. One patient underwent chemotherapy for Stage IV NSCLC and developed a primary (postpneumonic) empyema thoracis due to superinfection of the malignant pleural effusion. One patient had an infected postoperative haemothorax following open hearth surgey for aortic aneurysm rupture.

One patient developed empyema thoracis following Boerhaave syndrome. No patient had a BPF. Initially Mini-VAC therapy was used except in patient no. 6, who underwent previous conventional treatment consisting of a chest tube thoracostomy. Independent of the stage of empyema (acute or chronic), Staphylococcus, Streptococcus and anaerobic species were the most frequently isolated organisms. Additionally, Aspergillus fumigatus was found in 3 patients.

Table 3: Demographics of Mini-VAC patients

Patient number	**P1**	**P2**	**P3**	**P4**	**P5**	**P6**
Age/Sex	43♂	72♂	38♀	41♂	68♂	64♂
Karnofsky Index <50%	Yes	Yes	Yes	Yes	Yes	Yes
Comorbidity	Yes	Yes	Yes	Yes	Yes	Yes
Immunsupression	No	Yes	Yes	No	No	Yes
Primary Diagnosis	Aortic rupture-Haematothorax	NSCLC Stage IV	Rheumatic disease	Boerhaave-Syndrome	NSCLC Stage IA*	SCLC Stage IV*
Initial Surgery	Aortic reconstruction	Lobectomy	Wedge-Resection (VATS)	Decortication	Lobectomy (VATS)	Chest tube drainage

P: Patient, NSCLC: Non-small cell lung cancer, VATS: Video-assisted thoracoscopic surgery, *UICC 7th Edition

34

5.2.2. Surgical procedure (Mini-VAC, Figure 7)

Poor general condition of patients and inability to undergo extensive surgical procedure such as complete decortication, Mini-VAC therapy was initiated, as first described by Hofmann et al. [48]. Following minithoracotomy (a 5- to 6-cm incision for the thoracotomy without a rib spreader), the Alexis (Applied Medical, Rancho Santa Margarita, CA, USA) retractor was positioned. Following debridement, local decortication and flushing of the pleural space, the VAC sponges (black GranuFoam Standard Dressings, KCI Medical, Wiesbaden, Germany, 400–600 µm) were inserted through the Alexis retractor to fill the entire pleural cavity (Figure 6.). The level of suction was set to −75 mm Hg from the start and was increased slowly. Dressing changes were performed under anaesthesia in the operating theatre. All patients were treated with broad-spectrum antibiotics. The spectrum was modified in some cases based on the microbiological results. Antibiotic therapy was stopped when a wound swab showed no further pathogenic bacteria colonization (mean antibiotic therapy duration: 10.1 days).

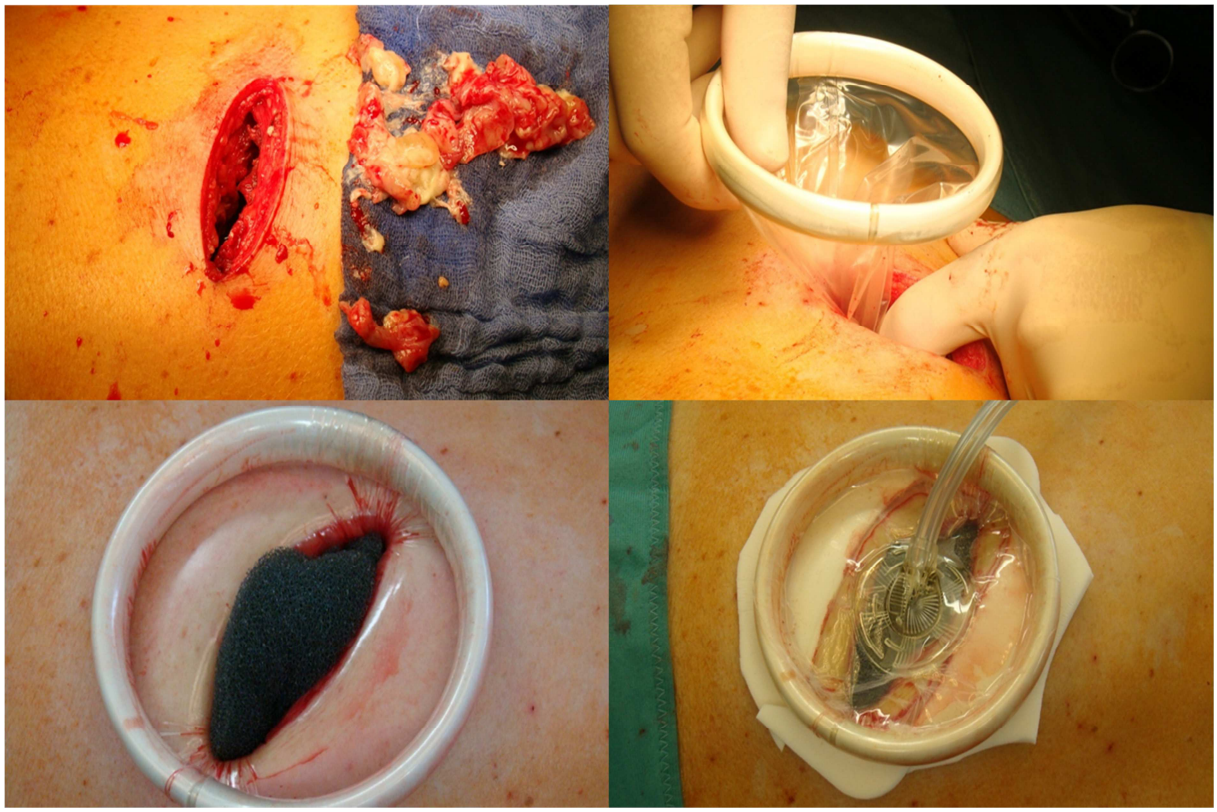

Figure 7: Mini-VAC procedure: mini-thoracotomy, debridement and local decortication, implantation of the soft tissue retractor, insertion of the vacuum foams and mobile suction.

5.2.3. Results of Mini-VAC therapy

Indications and time of Mini-VAC therapy

The indication for Mini-VAC installation was acute sepsis in patients with a poor general condition, failed primary conservative intervention (tube insertion) or complications of primary surgery (Table 4.). No patient had a detectable bronchopleural fistula. The median time between the initial surgery and Mini-VAC-Therapy was 26.5 (range 4–602 days).

Course of Mini-VAC therapy

Local control of the infection and control of sepsis were satisfactory in all 6 patients treated by Mini-VAC therapy. The patients tolerated a suction of – 75 ot - 125 mmHg and did not react with arrhythmia or haemodynamic complications due to the traction on the mediastinum during increases in suction. Membranes were not applied for the protection of the lung parenchyma. The suction used did not create any air leaks or bleeding from the lung or the mediastinal structures. At the time of VAC installation, two patients were in a severe clinical condition with acute respiratory insufficiency and mechanical ventilation. The two ventilated patients were weaned from ventilatory support 12 h after implementing Mini-VAC therapy. In these patients, Mini-VAC therapy allowed an improved re-expansion of the residual lung. In all cases, Mini-VAC therapy resulted in the rapid eradication of local infection. The patients underwent 2.5 ± 1.5 debridements and Mini-VAC changes (every third to fifth day) in the operation theatre under general anaesthesia. The Alexis retractor was also changed at this time. In most of the cases, only limited debridement was required at the Mini-VAC changes. After these procedures, the pleural cavity was visually and microbiologically determined to be clean. Antibiotics were withdrown when there were no signs of sepsis and the thoracic cavity had become sterile (mean time: 10.1 days).

Table 4: Mini-VAC indication, procedure and outcomes

Variable	**P1**	**P2**	**P3**	**P4**	**P5**	**P6**
Indication of Mini-VAC	P.o. Empyema	Sepsis Empyema	Sepsis Empyema	P.o. Empyema	P.o. Empyema	Primary Empyema
Onset	Acute	Chronic	Chronic	Acute	Acute	Chronic
Art of Intervention	Limited Decortication	Débrid.	Limited Decortication	Débrid.	Débrid.	Débrid.
P.o. mechanical ventilation after VAC	No	Yes (12 hours)	Yes (12 hours)	No	No	No
Number of VAC Changes in OR	1	2	4	2	2	3
Max. Suction mm Hg	- 75	- 125	- 125	- 125	- 100	- 100
VAC Duration, in days	4	12	18	9	11	9
Microbiology	Strep.	Staph.	Staph.	Staph. Pseudo.	Strep.	Enterobac. Asperg.
Length of Antibiotic Therapy, in days	10	12	7	6	7	19
Chest wall closed	Yes	Yes	Yes	Yes	Yes	Yes
Muscle Transposition	No	No	M. latissimus dorsi	No	M. latissimus dorsi	No
Outcome	Healed	Healed	Healed	Healed	Healed	Healed
Hospit. for VAC in days	22	33	29	11	24	12

Debrid.: Debridement, Hospit.: Hospitalization, P.o.: postoperative, Strep.: Streptococcus, Staph.: Staphylococcus, Pseudo.: Pseudomonas, Asperg.: Aspergillus

Outcome of Mini-VAC therapy

All patients were successfully treated by Mini-VAC intrapleural therapy (Table 5). After Mini-VAC treatment only 1 patient underwent a small wound infection healed by secondary intention. In most of the cases, the dimension of the pleural cavity was also decreased by Mini-VAC therapy. Only 2 patients had cavities that required a muscle flap closure. These two patients underwent a thoracomyoplasty by transposition of the the latissimus dorsi muscle. The chest wall was closed during the same hospital stay for all patients. All patients left the hospital in good health (Karnofsky index >70%) and with a sterilised cavity. The mean hospital stay after starting the VAC therapy was 22 ± 11 days. The patients were discharged with only oral non-steroidal anti-inflammatory drugs. No pleural empyema had recurred in any of the patients at the 3-month follow-up. All patients reported a very good quality of life in an outpatient interview. The short-term aesthetic results of Mini-VAC therapy are excellent (Figure 8).

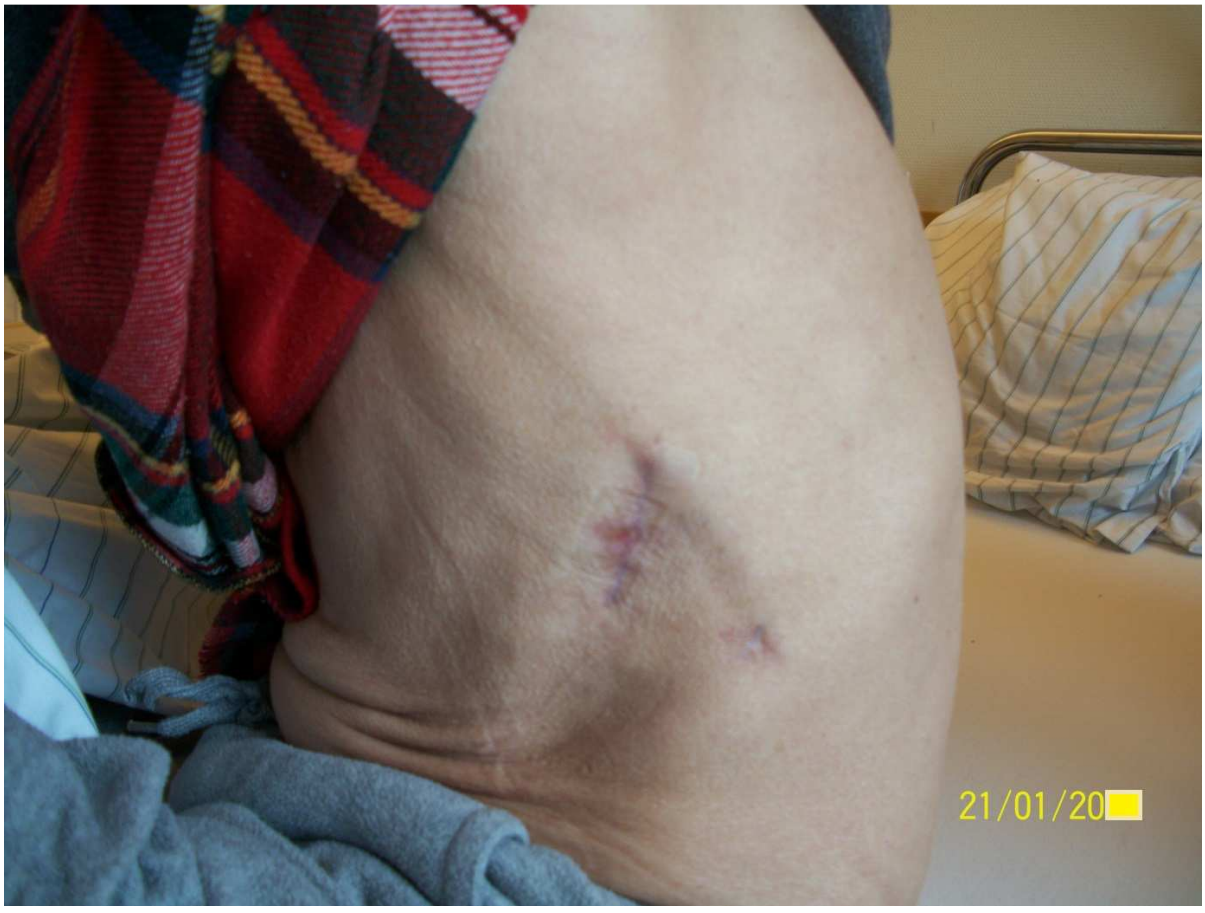

Figure 8: Postop. aesthetic results of Mini-VAC.

Table 5: Outcomes OWT+VAC vs. Mini-VAC

	Minimally invasive VAC therapy	OWT-VAC therapy	Autor, Year
Number of Patients	6	13	*Groetzner et al., 2009*
		8	*Sziklavari et al., 2011*
		11	*Palmen at al., 2009*
		27	*Saadi et al. 2009*
VAC therapy duration, in days (mean +/- SD, median – range)	11 +/- 7	64 +/- 45	*Groetzner et al., 2009*
		26,5 +/- 18,5	*Sziklavari et al., 2011*
		31 +/- 19	*Palmen at al., 2009*
		22 (range 5-66)	*Saadi et al., 2009*
Number of VAC changes in OR	2,5 +/- 1,5	n.a.	*Groetzner et al., 2009*
		2,5+/-2,5	*Sziklavari et al., 2011*
		0 (Changes on the ward)	*Palmen at al., 2009*
		6 (2 – 14)	*Saadi et al., 2009*
Hospital stay in days	22 +/- 11	44+/-34 (range 16-110)	*Groetzner et al., 2009*
		26,5+/-18,5	*Sziklavari et al., 2011*
		60+/-41	*Palmen at al., 2009*
		44,5 (range 20-114) median	*Saadi et al., 2009*
Survival (%)	100%	100%	*Groetzner et al., 2009*
		87,5%	*Sziklavari et al., 2011*
		100%	*Palmen at al., 2009*
		81%	*Saadi et al., 2009*
VAC related adverse event (%)	0%	0%	*Groetzner et al., 2009*
		0%	*Sziklavari et al., 2011*
		0%	*Palmen at al., 2009*
		3,7%	*Saadi et al., 2009*
Chest wall closure (%)	100%	100%	*Groetzner et al., 2009*
		71,4%	*Sziklavari et al., 2011*
		100%	*Palmen at al., 2009*
		100%	*Saadi et al., 2009*
Recurrence (%)	0%	15%	*Groetzner et al., 2009*
		0%	*Sziklavari et al., 2011*
		9%	*Palmen at al., 2009*
		3,5%	*Saadi et al., 2009*

5.2.4. Comment to Mini-VAC therapy

Following our first description of the feasibility of a new technique - Mini-VAC - in the treatment of pleural empyema [48], a series study was conducted. It was concluded, that all of the advantages of the VAC treatment with OWT are also offered by the Mini-VAC procedure.

Minimally invasive local decortication

The basic component of the Mini-VAC therapy is a plastic wound retractor that allows access to the pleural space without the need for a mechanical retractor. These retractors are routinely used in thoracic surgery for VATS surgery. The first instillation of the Mini-VAC system was performed under general anaesthesia, because the first operation also includes pus evacuation, debridement and flushing of the pleural cavity. The decision to perform local decortication only seems not to be disadvantageous. Similar lung re-expansion was achieved by debridement alone without decortication in patients presenting with empyema [63]. Neverthless, slow or minimum regression in the debridement group has also been observed [63].

VAC foam changes

The number of Mini-VAC changes in our group seems to be somewhat smaller as in OWT-VAC groups reported previously (Table 5) and, therefore, the Mini-VAC treatment time and hospital stays of these patients are shorter (Table 5.).

Wound closure

The decisive advantage of the Mini-VAC technique is the lack of a need for OWT with the classical rib resection. OWT is associated with more postoperative pain and a lower rate of permanent chest wall closure [9, 52, 79]. A persistent stoma with minimal drainage may remain, which increases the likelihood of secondary colonization by microorganisms [64]. Therefore, the best way to manage a persistent postempyema pleural space is by, e.g. muscle flap closure. Closure of the OWT

depends on the patient's individual concomitant diseases. Patient compliance (wisch to be operated) is also important.

The types and time of the closure strongly differ in the literature, especially for patients without VAC therapy. In the OWT-VAC study, the VAC-induced OWT was closed after a mean time of 3 months. Two patients refused the procedure. Groetzner et al. [58] performed direct surgical wound closure in all patients, but they used the VAC system for a mean period of 64 ± 45 (range 7–134) days. In the present study, all of the chest walls were closed after a mean time of 11 ± 7 days during the same hospital stay, and no further hospitalization was necessary. This very early closure was possible due to the fast local control of the empyema and the abdication of rib resection.
An additional advantage of plastic wound retractors use is that they act also as a barrier that protects the soft tissue and wound from bacterial translocation. This could also facilitaterapid and successful treatment making early closure possible.

Success of Mini-VAC

All patients left the hospital in good health (Karnofsky index >70%). Saadi et al. [65] reported an 82% survival rate. However, 5 of 27 patients died during or after OWT and VAC therapy, and there was one VAC-related complication.
The present Mini-VAC series success rate is substantially higher than that in groups with OWT and VAC treatment (Table 5).

5.2.5. Conclusions to Mini-VAC therapy

Mini-VAC therapy of complex pleural empyema is safe, rapid and successful. The greatest advantage of Mini-VAC is the avoidance of OWT, which enables a short treatment with subsequent early chest wall closure.

5.3. Mini-VAC-Instill Study

Open questions for the Mini-VAC treatment were in 2014 whether this new technique is applicable in patients with bronchopleural fistula, and whether simultaneous antibiotic/antiseptic flushing during VAC therapy is possible (VAC Instill). As the feasibility study of Mini-VAC-Instill [66] showed promising results, a prospective study was initiated.

5.3.1. Patients and methods

Study sample

From December 2012 to November 2014, 15 critically ill patients with empyema thoracis (primary, postoperative or recurrent pleural empyema) were scheduled for Mini-VAC-Instill therapy. The data had been collected prospectively. The study was approved by the Ethic Committee at the Hospital of the Brothers of Charity in Regensburg [56]. Inclusion criteria were as follows: poor general condition (Karnofsky index ≤50%) and multimorbidity (≥3 organ diseases) or immunosuppression (Figure 9).

The patients received treatment without classical thoracic fenestration by using intrapleural vacuum-assisted/instillation therapy dressing (V. A. C. VeraFlo; KCI Medical, Wiesbaden, Germany) for severe (Stage IIb–III; American Thoracic Society staging) pleural empyema.

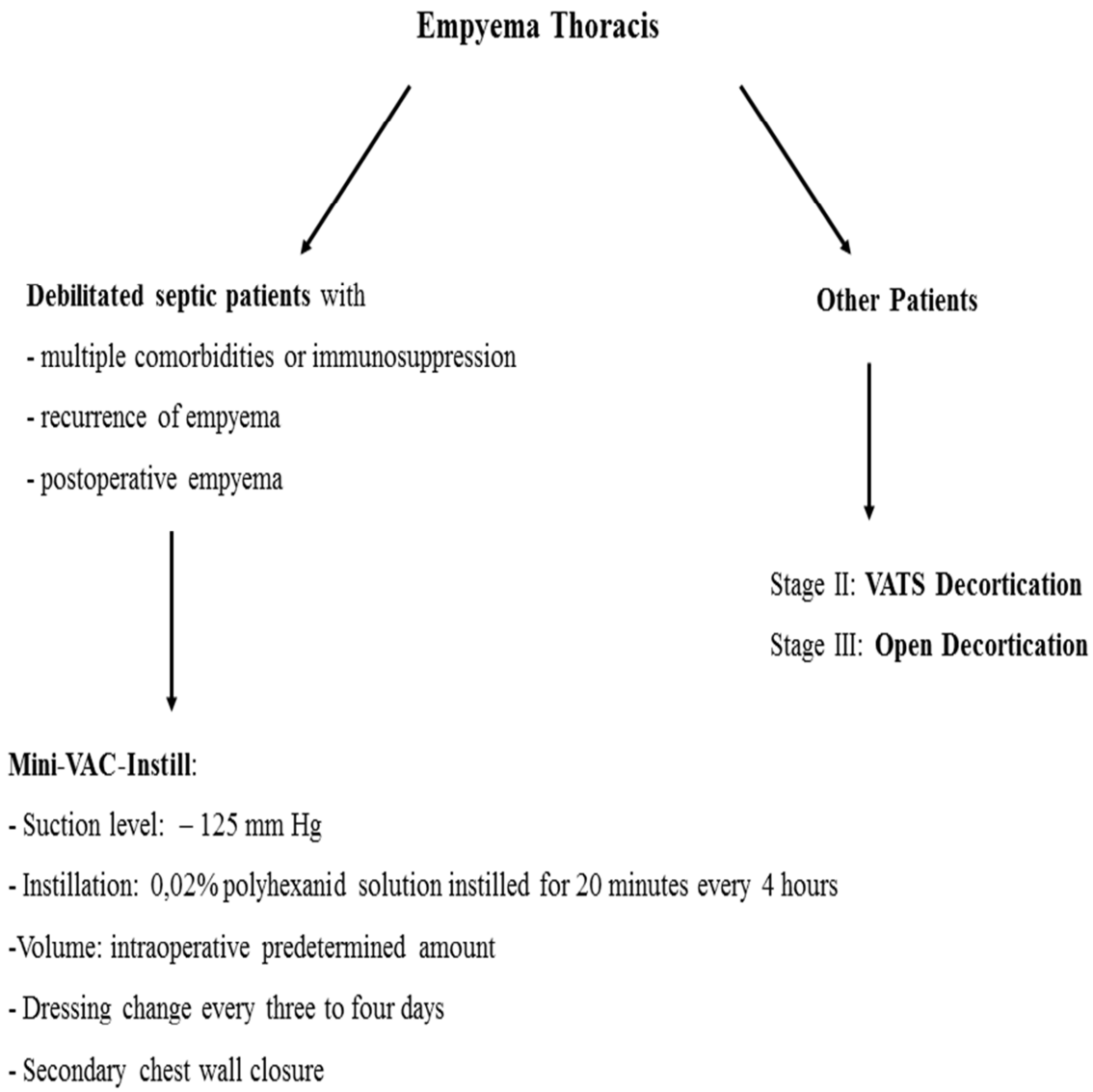

Figure 9: Decision making (2012-2014) algorithm for debilitated patients with empyema thoracis.

Patient demographics

The series consisted of 13 men and 2 women; the median age was 71 years (range, 25–91 years). The clinical characteristics of patients are given in Table 6. All patients had pleural empyema; among them, 7 presented with secondary (postoperative) empyema thoracis.

Two patients had undergone chemotherapy for advanced lung adenocarcinoma/gastric carcinoma with malignant pleural effusion and had

subsequently developed empyema due to superinfection of the malignant pleural effusion. One patient had a residual traumatic haematothorax and 5 patients developed empyema caused by parapneumonic effusion. The majority (4 of 7) of the post-thoracotomy empyemas occurred in the late postoperative phase (≥30 days). Eight patients received primary tube thoracostomy as a bridge to Mini-VAC-Instill procedure on the following day or a chest tube was inserted previously in an other institution.

In the remaining seven cases, we indicated the primary use of Mini-VAC-Instill for the therapy of the previously confirmed empyema.

Irrespectively to the length of the time of the infection, coccus bacilli were the most frequently detected microorganisms.

In addition, Fusobacterium sp. was identified in 1 patient and Parvimonas micra was found in another.

Table 6: Demographics of patients with Karnofsky ≤50%

Cause of empyema thoracis	**Multimorbidity**	**Immuno-suppression**	**Initial Surgery**	**Microbiology**	**Primary Management**	**Previous Antibiotic**	**ATS-Stage**
Primary empyema							
75-year-old man	yes	no	-	Escherichia coli	Tube drainage	Ceftriaxon/ Metronidazol	IIb
57-year-old man	no	yes	-	Escherichia coli/ Bacillus cereus	Tube drainage	Piperacillin/ Sulbactam	IIb
90-year-old man	yes	no	-	-	Tube drainage	Amoxicillin- clavulanic acid	IIb
71-year-old man	yes	no	-	Fusobacterium nucleatum	-	Piperacillin/ Tazobactam	IIb
75-year-old man	yes	no	-	Staphylococcus haemolitycus	-	Ampicilline/ Sulbactam	IIb
80-year-old man	yes	no	-	Haemophilus parahaemolyticus	-	-	IIb
35-year-old man	no	yes	-	Staphylococcus aureus	Tube drainage	Amoxicillin/Sulbactam	IIb
91-year-old man	yes	no	-	Escherichia coli	Tube drainage	AmpicillinTazobactam	III

Secondary (postop.) empyema							
87-year-old woman	yes	no	Vertebral spinal fusion	Staphylococcus aureus	Tube drainage	Piperacillin/ Sulbactam	IIb
25-year-old man	no	yes	S6-Resection	Actinomyces odontolyticus	-	Levofloxacin	IIb
73-year-old woman	no	yes	Lobectomy RUL	Staphylococcus aureus	-	Clindamycin	IIb
44-year-old man	yes	yes	Pleurectomy	Streptococcus dysgalacticae	Tube drainage	Amoxicillin- clavulanic acid	IIb
70-year-old man	yes	yes	Lobectomy RUL	Pseudomonas aeruginosa*	-	Piperacillin/ Sulbactam	IIb
61-year-old man	yes	yes	Oesophagus-resection	Streptococcus intermedius	Tube drainage	Piperacillin/ Tazobactam	IIb
60-year-old-man	no	yes	Pneu-mectomy	Staphylococcus/ Parvomonas micra	-	-	IIb
*RUL: right upper lobe, *4MRGN, ATS: american thoracic society.*							

5.3.2. Surgical procedure (Mini-VAC-Instill)

Considering the critical general condition of patients and aiming a fast track eradication, the patients were treated with the Mini-VAC-Instill therapy, with 0.02% polyhexanide solution instilled for 20 min every 4 h (Figure 10).

The empyema sack was identified and targeted by computer tomography. Bronchoscopy was carried out preoperatively in all cases in order to exclude significant airway obstruction or BPF (e.g. after a thoracic operation).

Under general anaesthesia, a 5- to 6-cm-long incision was performed. Previous thoracotomy incisions were avoided because the empyema thoracis were significantly inferior to the primary thoracotomy.

After a mini-thoracotomy with no rib-spreading technique, the empyema cavity was opened (Figure10), followed by intercostal aspiration of all pus and necrotic debris.

The surrounding lung was adherent to the parietal pleura, creating an isolation barrier.

The cavity was flushed with 0.02% polyhexanide (Lavanid; Serag-Wiessner KG, Naila, Germany). A flexible polymer membrane retractor (Alexis, Applied Medical Resources Corporation, Rancho Santa Margarita, CA, USA) was inserted. The retractor provided 360° of circumferential, atraumatic retraction with sufficiently wide opening of the pleural cavity (Figure 10).

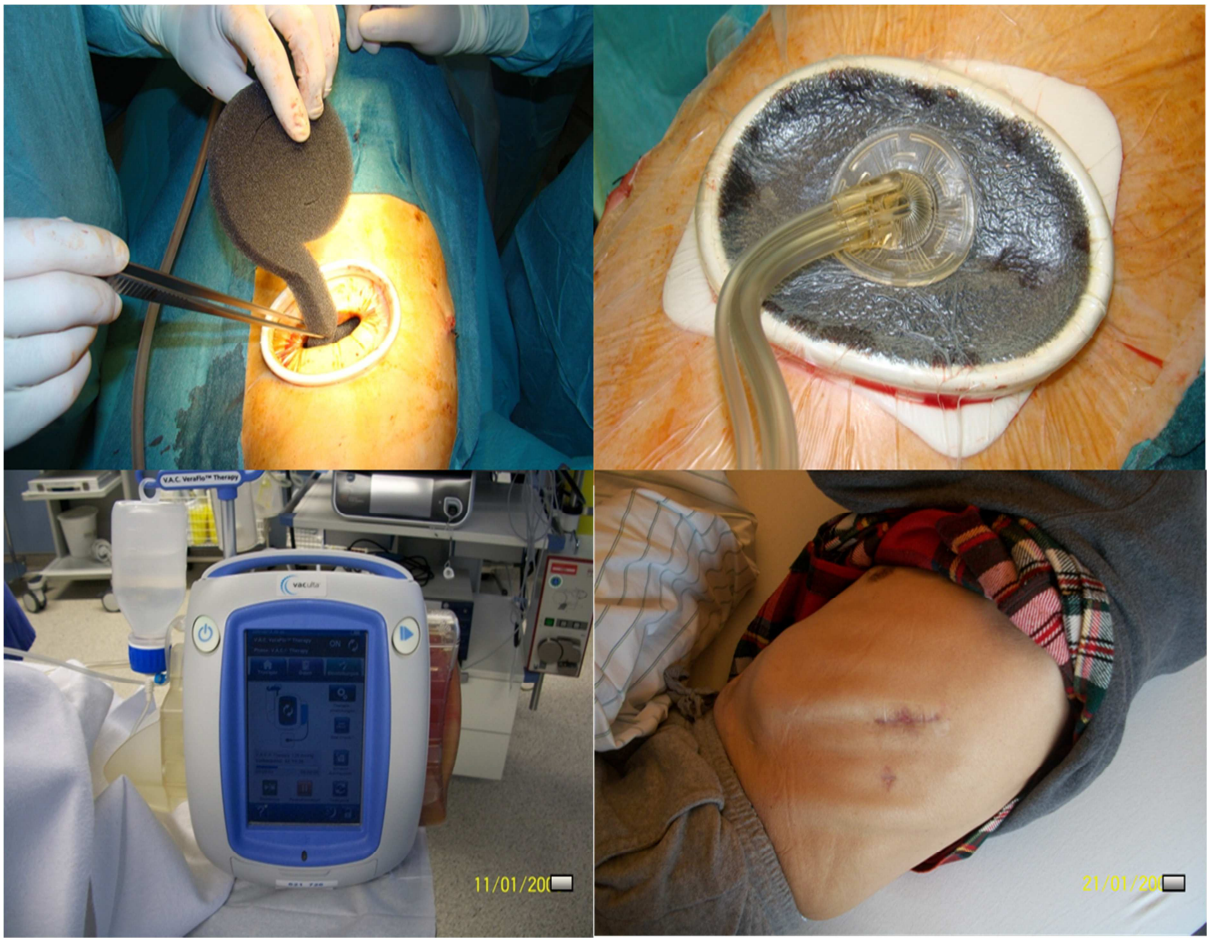

Figure 10: Mini-VAC-Instill: minimally invasive local decortication, vacuum foam insertion and periodic polyhexanid instillation, good aesthetic results.

The volume of the residual pleural space was determined during lung expansion, and the wound volume determined the amount of fluid instilled.

Following debridement and local decortication, a VAC sponge (black polyurethane ester dressing, 600 microns, relative hydrophobicity of 2; KCI Medical, Wiesbaden, Germany) was introduced in the pleural cavity over the wound protector to obliterate the residual intrathoracic space (Figure 11A-B).

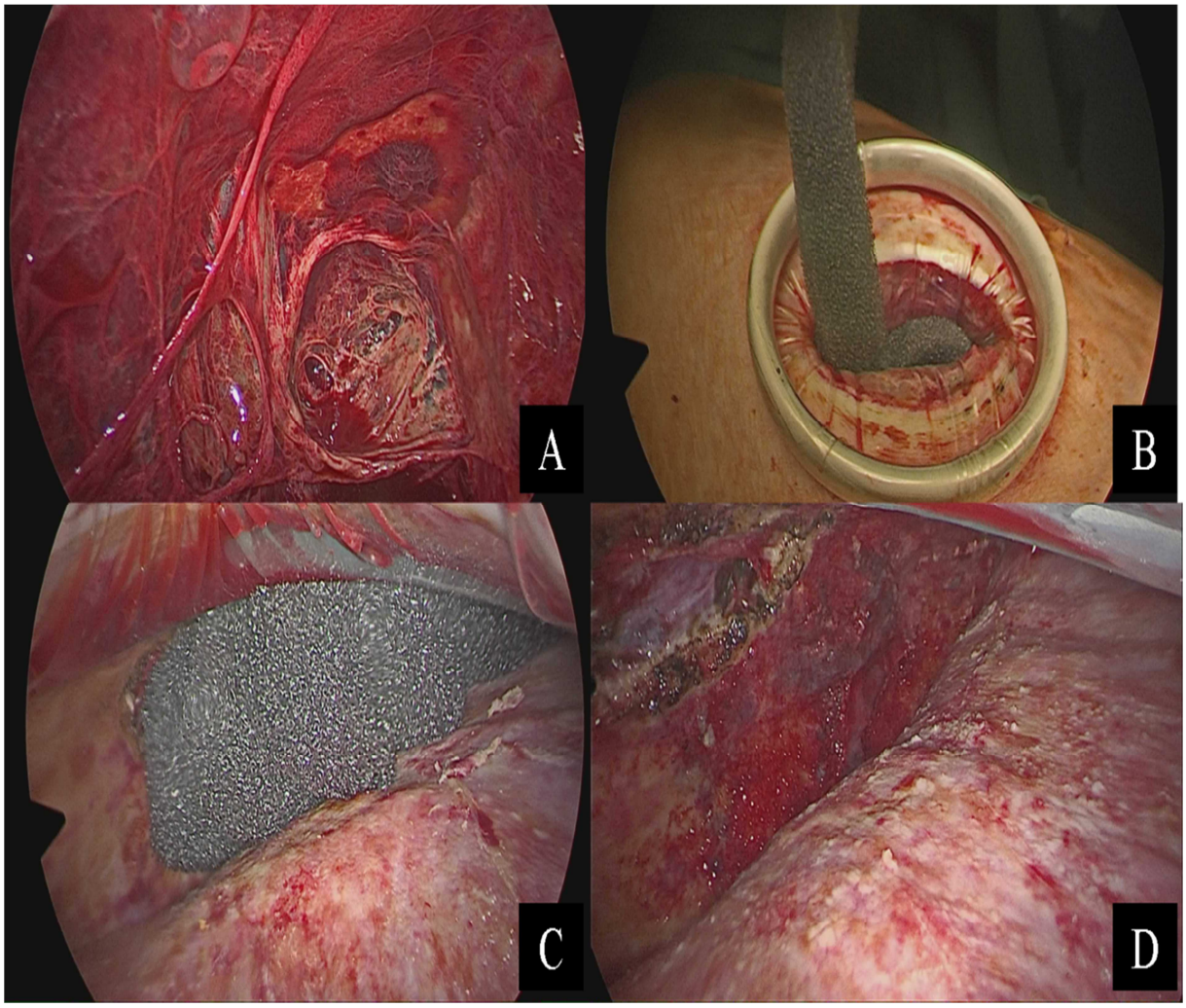

Figure 11 (A) Empyema thoracis Stage II, (B) Introduction of VAC-Instill sponge over Alexis retractor (C) Intrapleural VAC-Instill, (D) Postvacuum thoracoscopic view.

The VAC-Instill pad, including the tubing, was positioned on top of the sponge.

Foam pads were used under the ring to prevent decubitus.

The negative pressure was set at −75 mmHg from the beginning and it was later increased up to – 125 mmHg.

Flushing of the pleural cavity was automatically with a predetermined amount (intraoperative measured ml) of 0.02% polyhexanide in a topical solution delivery mode (20 min instillation time every 4h, Figure 12).

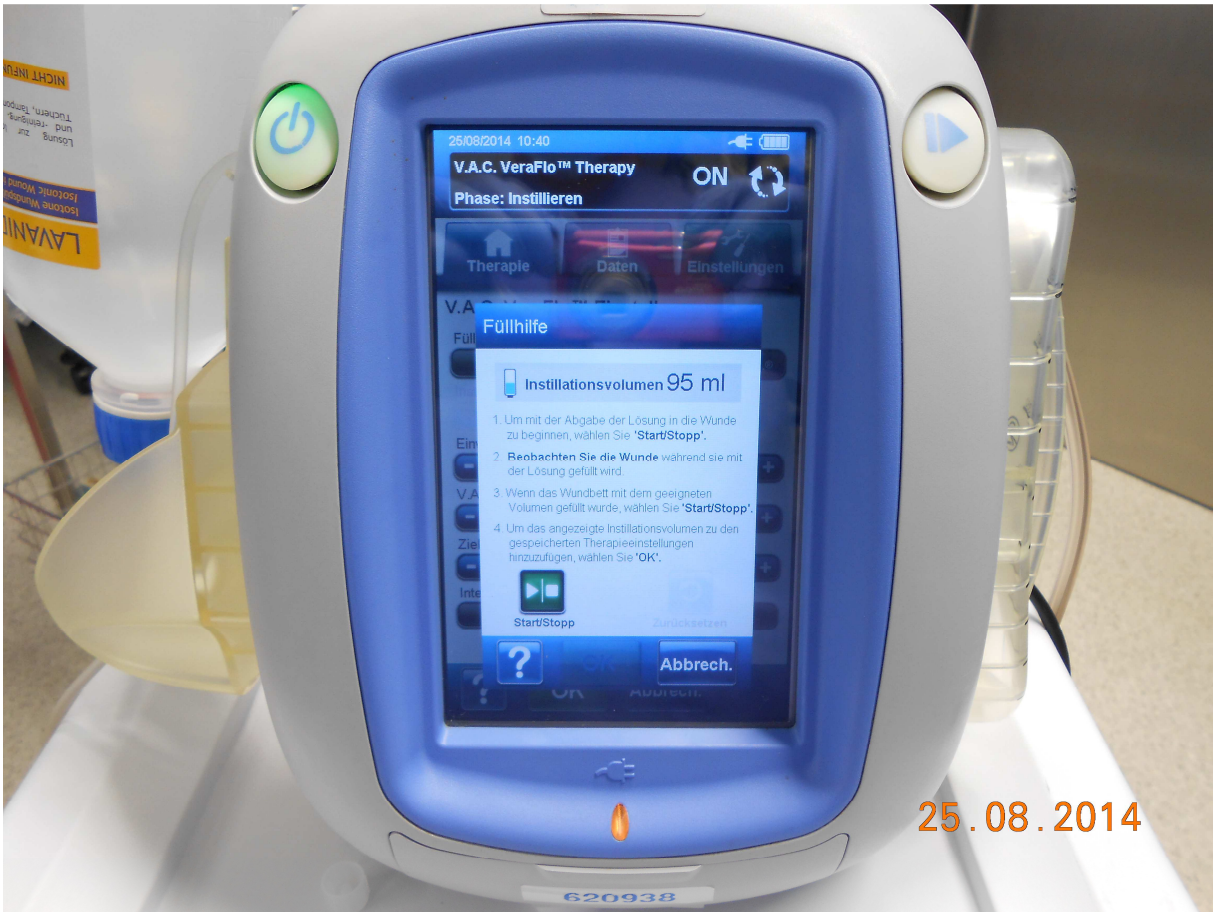

Figure 12: automated topical solution delivery mode, here for example 95 ml polyhexanide instillation for 20 min every 4 h.

The patients were treated ex juvantibus with broad-spectrum antibiotics. Based on the microbiological results, the substance spectrum was occasionally adapted. The Mini-VAC-Instill system was changed every 3–4 days in the operating theatre (OT) under a short intravenous propofol anaesthesia (TIVA). Only a minimum debridement was performed at each sponge change (Figure 11C). When the thorax cavity was macroscopically peaceful (Figure 11D.) and the patients had two microbiological negative cultures, the remaining pleural space was filled with a hemostyptic collagen sponge that contained the aminoglycoside antibiotic gentamicin (Genta-Coll resorb; Resorba GmbH, Nürnberg, Germany).

Genta-coll sponge may absorb large quantities of fluid. During this absorption process, bacteria and fibrin clots were also removed. The wound was then closed with single stitches. After the Mini-VAC-Instill therapy, the remaining pleural space was small in all but one case (mean volume ≤303 ml). When necessary, the antibiotic

therapy was maintained per os throughout the duration of the Mini-VAC-Instill therapy and was stopped 2 weeks after the start of the therapy, when the pleural space had become clean (13 days; range, 8–21 days, Figure 11D.).

5.3.3. Results of Mini-VAC-Instill

Indications and timing of Mini-VAC-Instill therapy

Acute empyema thoracis patients without BPF and septic schock were involved. Failed previous conservative therapy (thoracic drainage) and complications from previous thoracic surgery were the main indication. Empyema thoracis developed median on the 26th postoperative day (range, 4–54 days after initial surgery).

Course of Mini-VAC-Instill therapy

Mini-VAC-Instill therapy was effective in all 15 patients with respect to local and systemic infection control. With a maximum suction of –125 mmHg no haemodynamic or respiratory complications due to traction on the mediastinal structures were observed. Four patients had a detectable air leakage during the first three days with decreasing tendency. Specific covering of the lung surface was not necessary. Relevant air leaks or bleeding complications due to intrathoracic suction therapy did not occur. No patient developed systemic symptoms due to the instillation of the 0.02% polyhexanide solution. We have not seen a negative effect of VAC-Instill therapy on the pleural carcinosis; both patient´s empyema healed. The patients underwent a median of 1 (range, 1–5) round of debridement and operative dressing change (usually twice a week, on Tuesdays and Fridays) using laryngeal mask ventilation and a short-acting anaesthetic. Changing of the Alexis ring and wound debridement were performed.

Atibiotics were withdrawn as the thoracic cavity had become sterile, and the C-reactive protein levels fell below 100 mg/l (mean time, 13.15 days; range, 8–21 days). Complete sterilization was achieved in 13 of 15 patients. No closure of the chest wall was decided in one patient and one patient underwent fenestration secondary due to subacute recurrence. Those 2 patients had residual volumes of 400

and 500 ml, respectively. Re-expansion of the remaining lung parenchyma was observed during the therapy with Mini-VAC-Instill. In order to achieve coverage of the pleural cavity by granulation tissue, vacuum therapy of 9 days (range, 5–25 days) was necessary.

Outcome of Mini-VAC-Instill therapy

The median hospital stay after secondary chest wall closure was 6 days (range, 2–17 days; Table 7). The patients were in this period fully mobilized. In-hospital mortality was 6.7% (n=1) and was due to asystolia, unrelated to VAC therapy. Sterlility of the cavity and closure of the chest cavity during the same hospital stay without recurrence was achieved in 80% (13 of 15) of all cases. In 2 patients, we performed finally OWT because of permanent bacterial colonization. One patient developed wound dehiscence. In most of the cases, the dimension of the pleural cavity was also decreased by the Mini-VAC-Instill therapy.

No cavities required muscle flap for closure. The mean residual intrathoracic volume was 303 ml (range, 50–700 ml). The patient with a 700-ml residual intrathoracic volume had previously undergone a pneumectomy and a transposition of the latissimus dorsi muscle. All but one patient was discharged with a good general condition (Karnofsky index >70%) and only an oral non-steroid anti-inflammatory drugs.

After the follow-up at an average of 13.2 months (range, 3–25 months), pleural empyema recurred in only one of the surviving 14 patients, 21 days after discharge. Two patients died in the late postoperative period (Day 43 and Day 100, respectively, after discharge) of fulminant urosepsis and carcinoma-related multiorgan failure, respectively.

Analysis of the follow-up interviews in the outpatient clinic showed a good quality of life and an acceptable subjective aesthetic result.

Table 7: Mini-VAC-Instill and outcomes

Cause	Mini-VAC-Instill changes in OR (number)	Mini-VAC-Instill duration (days)	Residual volume (ml)	Thoracic cavity sterile	Chest wall closed	Hospit. after chest wall closure (days)	Outcome
Primary empyema							
75-year-old man	1	5	200	Yes	Yes	5	Healed
57-year-old man	3	12	150	Yes	Yes	4	Healed*
90-year-old man	2	14	180	Yes	Yes	-	In hospital death
71-year-old man	2	10	290	Yes	Yes	7	Healed
75-year-old man	5	25	310	Yes	Yes	3	Recurrence
80-year-old man	1	7	550	Yes	Yes	3	Healed
35-year-old man	3	14	260	Yes	Yes	2	Healed
91-year-old man	1	8	500	No	No	5	OWT-healed
Postop. empyema							
87-year-old woman	2	10	50	Yes	Yes	7	Healed*
25-year-old man	1	8	300	Yes	Yes	10	Healed
73-year-old woman	1	8	230	Yes	Yes	11	Healed
44-year-old man	1	8	150	Yes	Yes	17	Healed
70-year-old man	3	15	400	No	No	10	OWT-healed
61-year-old man	1**	9	310	Yes	Yes	7	Healed
60-year-old-man	1	7	700***	Yes	yes	4	Healed

Hospit.: Hospitalization, *death in the late postoperative phase and not related to empyema; **sponges were changed once on the ward; ***previously, pneumonectomy and latissimus dorsi muscle flap transposition; OWT: open window thoracostomy

5.3.4. Comment to Mini-VAC-Instill therapy

VAC and instillation of antiseptics

In cases of active pleural empyemas, flushing (lavage) via a chest tube or the OWT is often necessary. In contrast to low-pressure lavage and other irrigation techniques that wash or flush a wound using a continuous stream of liquid, instillation introduces a topical solution into a wound and allows the solution to stand in the wound for a period of time prior to fluid removal. The use of a soak phase is an important distinction between continuous irrigation and periodic instillation and may be a key differentiator between low-pressure lavage and the Mini-VAC-Instill method. In a separate study by Allen et al. [68], the cleansing ability of low-pressure lavage and instillation were compared in a porcine wound model. The results supported the utility of a soak phase during VAC-Instill that allows for loosening of soluble debris that can then be removed during the negative pressure phase of therapy. While complete wound bed coverage is certainly achievable with manual systems, cleansing may be challenging in larger wounds or wounds with complex geometries [68].
The bacteriology of empyemas is often polymicrobial mixed, not rarely multiresistant and the mortality rate of patients with aerobic Gramnegative bacilli isolated is around 25% [69-70]. Antibiotics in infected pleural fluid may be inactivated in the presence of pus, low pH or beta-lactamase enzymes. On the other hand, the instillation of local antiseptics leads to an immediate local effect that is pH independent, indicating they are true germicides. As a result of the topical instillation, complete sterilization was achieved in 87% of our patients (13 of 15) within a median of 9 days. In contrast, Saadi et al. [65] observed complete sterilization in only 33% (7 of 21) of cases after a median of 22 days of VAC therapy without instillation.

Results of Mini-VAC-Instill

The use of VAC therapy in combination with instillation in a large patient group with pleural empyema has only been described once before in 2013, when Schreiner et al. [71] published results from 11 patients undergoing surgery for thoracic sepsis. Seven of these had pleural empyema. The patients were treated with polyhexanide

solution, and vacuum therapy was performed for 6.5 ± 1.7 days. In 2 of 11 cases, the combination therapy was repeated. In 91% (10/11) of the patients, sterile wound status was achieved before secondary wound closure. This study showed also that patients treated with the combination therapy required fewer days of treatment (6.5 ± 1.7 days) compared with patients treated with VAC therapy without instillation; median, 22 days; range, 5–66 days) [65].

In a non-randomised comparative retrospective study the instillation group was in-hospital mortality free in comparison to 19% of the control [65]. Our findings are consistent with those of Schreiner et al., who concluded that complicated and chronically infected residual cavities are possible indications for Mini-VAC-Instill therapy. In the group of patients of Schreiner et al., all wounds underwent secondary closure without recurrence, and flap transposition was performed in 43% of the patients. In our group, no tissue obliteration was performed, because the remaining pleural space was small (mean, ≤303 ml) in all but one case after the Mini-VAC-Instill therapy.

The absolute success rates in the two groups were similar (71.4% vs 80% healed after chest wall closure). In addition, the absolute success rate of empyema treatments and closure of chest walls that were completed under our supervision were as high as the success rates from other studies using VAC therapy with instillation and which reported a substantially higher rate of success than groups treated with only OWT or VAC in conjunction with OWT [40, 57]. In addition, since the introduction of the Mini-VAC-Instill therapy, when the thoracic cavity became sterile, all chest walls were closed during the same hospital stay.

The frequency of vacuum-dressing changes in our report was somewhat smaller than those reported for other studies and so the therapy duration and length of stay in hospital in our group were understandably shorter (Table 8.).

Air leakage

Our starting level of negative pressure was −75 mmHg. This negative pressure was successively increased to −125 mmHg over time, and air leakage was not a contraindication.

Question of Mini-VAC-Instill in outpatient setting

Some authors and we as well [7, 54, 72] described OWT-VAC therapy in an outpatient setting. In our opinion, the Mini-VAC-Instill dressings should be routinely changed every 3–4 days, in the OT, to allow precise and continued monitoring of infection. This means that repeat debridement treatment can be performed as required to keep the wound bed clean for optimal healing. In addition, the most common complication when using VAC therapy is pain, especially during dressing changes and initial application of vacuum. Systemic premedication or injection of topical anaesthetic into the VAC system prior to dressing change often allows dressing changes to be performed at the bedside [73]. Nevertheless, for intrathoracic wounds a short general anaesthesia with laryngeal mask airway ventilation in the OT may be more suitable. The Mini-VAC-Instill requires dedicated perioperative care and tools, therefore it is not recommended in outpatient setting.

Table 8: Overview Mini-VAC-Instill vs standard Mini-VAC/OWT-VAC Therapy

Author/Year/Technique	N=	BPF (%)	Chest wall closure (%)	Succes rate of chest wall closure (%)	Absolute success rate (%)	30-day hospital mortality	OWT-Duration (days)	Flap-Tansposition (%)
OWT-VAC								
Groetzner et al. 2009	13	8%	85%	100%	85%	0%	m 64	16%
Palmen et al. 2009	11	0%	100%	91%	91%	0%	m 39	82%
Al-Mufarrej et al. 2010	6	67%	67%	100%	67%	0%	m 64	100%
Aru et al. 2010	5	80%	100%	100%	100%	0%	M 48+*	25%
Sziklavari et al. 2011	8	25%	62,5%	100%	62,5%	0%	m 97,8	37%
Saadi et al. 2011	27	19%	81%	100%	81%	19%	M 22	67%
Celik et al. 2012	9	22%	100%	89%	89%	11%	m 36,5	22%
Begum et al. 2012	10	0%	0%	90% s*	90%	10%	r 30-210	0%
Mini-VAC								
Sziklavari et al. 2013	6		100%	100%	100%	0%	m 11,7	33%
Mini-VAC-Instill								
Schreiner et al. 2013	7	0%	71,4%	100%	71,4%	14%	M 7	43%
This study	15	0%	87%	92%	80%	6,7%	M 9	0%

BPF: bronchopleural fistula, OWT: Open Window Thoracostomy, Absolute success rate: chest wall closure (%) x success rate of chest wall closure (%), M: median, m: mean, r: range, 48*: hospitalization + home (outpatient) management, s*: spontaneous.

5.3.5. Conclusion to Mini-VAC-Instill therapy

Mini-VAC-Instill therapy allows automatic local instillation of antiseptic fluids in the infected cavity, following continuous drainage and suction for the purpose of cleaning and healing empyema.

For debilitated empyema patients with poor general condition and sepsis, standard videothoracoscopic or open surgical methods are often too invasive. Mini-VAC-Instill procedure in these high-risk patients is less demanding, therefore recommendable. This technique is safe and highly compatible with high-risk patients. Contraindications of the therapy are coagulopathy, permanent pain and allergic reaction to the materials.

Accumulated evidence in this issue topic, although limited, suggests that the Mini-VAC can potentially alleviate morbidity and decrease the length of the hospital stay in selected patients with empyema.

These results have yet to be proven by larger studies and clinical trials.

6. *Overview of VAC modalities; a comparative sequential analysis*

The report on 43 high risk empyema thoracis patients includes debilitated and/or septic patients with pleural infection of various etiologies. The aim of this retrospective study is to determine the effectiveness of intrathoracic negative pressure therapy in empyema treatment and the comparison of the short-term and long-term outcomes of the different intrapleural VAC techniques applied.
The question is whether Mini-VAC(-Instill) is superior to open window thoracostomy with vacuum assisted closure in the management of primary and postoperative empyema thoracis.

6.1. Patients and methods

Patients

Between September 2009 and December 2014, 379 consecutive patients had been treated for primary and secondary pleural empyema at the Center of Thoracic Surgery in Regensburg, Germany (Krankenhaus Barmherzige Brüder Regensburg, University Medical Center Regensburg). Among them, 43 patients were treated by intrathoracic VAC therapy. Indication for intrathoracic VAC treatment was empyema thoracis and poor general condition (Karnofsky index ≤50%) with multimorbidity (≥3 organ diseases) or immunosuppression.
The medical records of all patients were reviewed; no patient was excluded. The study was reviewed and approved by the Ethics Committee of the University of Regensburg (approval number: 15-101-0265).

Clinical features

Parameters as well as demographic and clinical characteristics are summarized in Table 9. 17 of 43 patients (40%) had presented with parapneumonic or postpneumonic empyema. 26 of 43 patients (60%) had postoperative pleural

empyema, of whom 6 patients presented with postpneumonectomy (3 of these 6 patients had undergone completion pneumectomy due to postresectional empyema), 5 with postresectional empyema, and 5 with bronchopleural fistula. 2 patients had esophago-pulmonary fistula. The remaining 8 patients had developed empyema after thoracic surgery. Indication for surgery was thoracic empyema at ATS stage II (n = 37) and stage III (n = 6) and pre-septic or septic condition. 4 patients had developed septic shock.

A refinement of techniques process

The patients were grouped according to the VAC treatment modality received (OWT-VAC vs. Mini-VAC vs. Mini-VAC-Instill). Grouping was done by chronologic selection and there was an organic progress from one technique to the next one: OWT-VAC (n = 20) procedures were carried out between 2009 and 2011, Mini-VAC (n= 8) between 2011 and 2013, and Mini-VAC-Instill (n = 15) from 2014 onwards. The three groups did not substantially differ with regard to clinical features (Table 9). Some evaluations were also conducted according to the genesis of pleural empyema (primary vs. secondary).

Summary of operative technique

OWT-VAC group (2009 to 2011, n = 20).

Mini-VAC group (2011 to 2013, n = 8).

Mini-VAC-Instill group (2013 to 2014, n = 15).

Table 9: Non parametic patient demographics, distribution of clinical features and samples of OWT-VAC, Mini-VAC, and Mini-VAC-Instill

Baseline characteristic	OWT-VAC (n=20)	Mini-VAC (n=8)	Mini-VAC-Instill (n=15)	Total (n=43)	p-value
Age [years], mean (range)	65 (39-85)	57 (43-68)	67 (25-91)	64 (25-91)	0.243[A]
Sex, n (%)					0.237[C]
women	1/20 (5%)	0/8 (0%)	3/15 (20%)	4/43 (9%)	
men	19/20 (95%)	8/8 (100%)	12/15 (80%)	39/43 (91%)	
Multimorbidity (n>3)	15/20 (75%)	7/8 (88%)	10/15 (67%)	32/43 (74%)	0.534[C]
Empyema side, n (%)					*0.039*[C]
Right	11/20 (55%)	3/8 (38%)	13/15 (87%)	27/43 (63%)	
Left	9/20 (45%)	5/8 (62%)	2/15 (13%)	16/43 (37%)	
Immunosuppression, n (%)	8/20 (40%)	4/8 (50%)	7/15 (47%)	18/43 (42%)	0.851[C]
Previous antibiotics, n (%)	11/20 (55%)	7/8 (88%)	10/15 (67%)	28/43 (65%)	0.285[C]
Malignancy	11/20 (55%)	3/8 (38%)	5/15 (33%)	19/43 (44%)	0.443[C]
Empyema genesis, n (%)					0.057[C]
Primary	4/20 (20%)	5/8 (62%)	8/15 (53%)	17/43 (40%)	
Secondary-postoperative	16/20 (80%)	3/8 (38%)	7/15 (47%)	26/43 (60%)	
ATS empyema stage, n (%) Stage I	none	none	none	none	0.464[C]
Stage II	17/20 (85%)	8/8 (100%)	12/15 (80%)	37/43 (86%)	
Stage III	3/20 (15%)	0/8 (0%)	3/15 (20%)	6/43 (14%)	
Recurrent empyema with previous treatment, n (%)	13/20 (65%)	7/8 (88%)	8/15 (53%)	28/43 (65%)	0.285[C]

A: ANOVA, C: Chi: Exact Pearson's chi-squared Test

All patients were intravenously treated with antibiotics; if necessary, treatment was adapted and occasionally modified according to antibiogram results. When the cavity became sterile, antibiotics were discontinued after futher 7 days.
In case of BPF, the stump was closed by circumferential suturing of an intra- or extrathoracic muscle flap or pericardial fat flap. In patients with post(bi)lobectomy empyema in association with necrotizing pneumonia, surgical management consisted of completion pneumectomy (n = 3) and muscle flap or pericardial fat flap transposition followed by intrathoracic VAC therapy.
In the absence of BPF, debridement and local decortication were performed before negative pressure wound therapy. To avoid direct contact of the VAC device with the mediastinum after lobectomy and pneumectomy, the area was covered with Mepitel (Mölnlycke Health Care, Erkrath-Unterfeldhaus, Germany) during the first session.

6.2. Preconditions for secondary chest wall closure

Empyema management techniques — chest closure including — vary, but they all include debridement, cleaning and obliteration of the pleural cavity to eradicate infection. The main factors in the treatment of complex pleural empyemas are the cleaning of the pleural space and the development of granulation tissue. Local insertion of an antibiotic sponge after Mini-VAC-Instill supports this anti-infection process and also fills the pleural cavity.
However, in our view, the obliteration of the pleural space has a minor role in the healing of empyema. Chest wall closure required two sterile ultures and complete macroscopic cover of granulation tissue of mediastinal and visceral pleura (Figure 13). Furtehrmore, the presence of viable tissue due to manipulation was eligible.

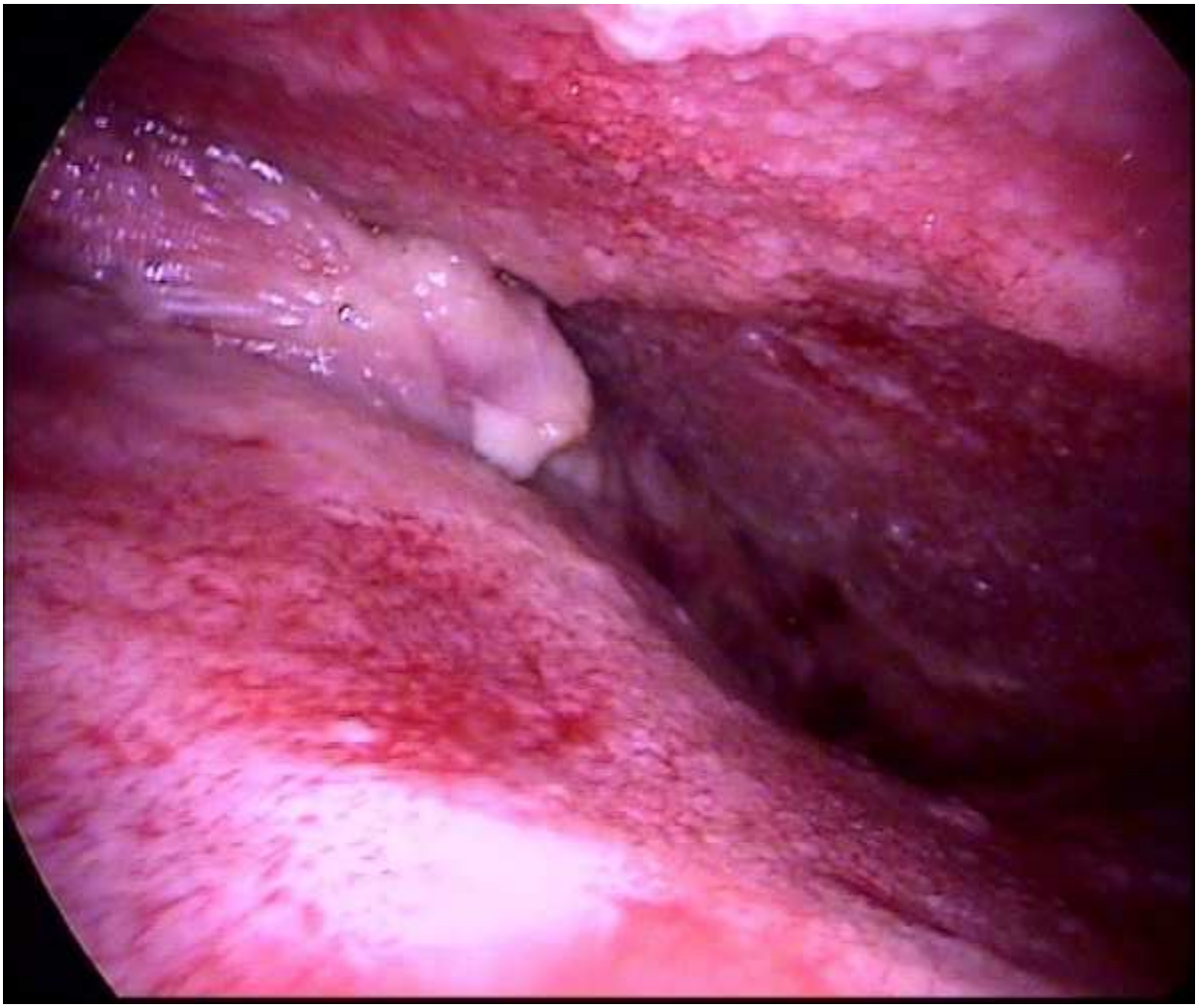

Figure 13: Intrathoracic macroscopic view after VAC therapy: very good diffuse granulation.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or range, categorical variables as absolute numbers and relative frequencies.

Categorical variables were compared with Chi-square tests. Differences in the duration of intrathoracic vacuum therapy and length of hospital stay among the different surgical techniques were analyzed using analysis of variance (ANOVA). Estimated marginal means (EMM) of the duration of vacuum therapy and the length of hospital stay − adjusted by the type of surgical indication (primary vs. postoperative empyema) − were computed and compared among the different surgical techniques. Paired differences and the corresponding 95% confidence intervals are presented as effect estimates.

Overall survival time was defined as the date of commencing OWT-VAC or Mini-VAC (Instill) treatment to the date of death or the last follow-up. Univariate Cox proportional hazard models were used to analyze the relationship between overall survival and the variables of age, malignancy, surgery indication, empyema treatment, and successful chest wall closure. Hazard ratios and corresponding 95% CIs are presented as effect estimates. A p-value of < 0.05 was considered statistically significant. Due to the exploratory nature of this study, no adjustments for multiple testing were made. All statistical analyses were done with the IBM SPSS software program Version 23.0 (IBM Corporation, Armonk, New York, United States).

6.3. Results

All three subgroup preselection features were statistically equal, therefore outcome comparations are well substantiated and valid.

6.3.1. Short-term outcomes

The most common causative organisms of empyema thoracis in the series was an infection due to facultative anaerob bacteria presence (Table 10).

Table 10: Causative organisms of lung infections (n=43)

Anaerob bacteria	n=4
Aerob bacteria	n=4
Facultative Anaerob bacteria	n=30
Fungal infection	n=2
not confirmed	n=3

Overall, the mean duration of intrathoracic vacuum therapy was 14 days, ranging from 5 to 48 days. Paired comparison of the VAC procedures (Table 11) showed that the mean vacuum duration in the Mini-VAC and Mini-VAC-Instill groups (12.4±5.7 and 10.4±5.4 days) was significantly shorter than that in the OWT-VAC group (20.3±9.4 days).

The mean durations of VAC in the primary empyema group and postoperative empyema group were almost equal (14.4 days vs. 14.3 days; p = 0.968).

Table 11: ANOVA post-hoc pairwise comparisons of OWT-VAC, Mini-VAC, and Mini-VAC-Instill regarding vacuum duration and length of hospital stay

	Vacuum duration in days*		
Pairwise therapy comparisons	**Estimated marginal means**	**Difference (95%-CI)**	**p-value**
OWT-VAC vs Mini-VAC	20.3 vs 12.4	7.9 (1.0; 14.8)	**0.026**
OWT-VAC vs Mini-VAC-Instill	20.3 vs 10.4	9.9 (4.27; 15.5)	**0.001**
Mini-VAC vs Mini-VAC-Instill	12.4 vs 10.4	2.0 (-4.9; 8.8)	0.565
	Postoperative length of stay in hospital in days**		
Pairwise therapy comparisons	**Estimated marginal means**	**Difference (95%-CI)**	**p-value**
OWT-VAC vs Mini-VAC	24.4 vs 23.7	0.7 (-8.7; 10.1)	0.881
OWT-VAC vs Mini-VAC-Instill	24.4 vs 15.6	8.8 (1.1; 16.6)	**0.027**
Mini-VAC vs Mini-VAC-Instill	23.7 vs 15.6	8.2 (-0.8; 17.1)	0.074

95%-CI: 95% confidence interval; *Main effects: Vacuum duration (p=0.003), surgery indication (p=0.968); **Main effects: Vacuum duration (p=0.052), surgery indication (p=0.744)

No major complication was related to intrathoracic VAC therapy. The median occasion of VAC system changes was 2 (range: 1 to 6 changes).

In the OWT-VAC group, the chest wall was closed secondarily after recovery in 12 (60%) of 20 patients (Table 12).

In the minimally invasive vacuum therapy groups, all patients but one underwent primary chest wall closure during the same hospital stay (22 of 23, 96%).

Table 12. Pairwise comparison of different OP procedures for primary chest wall closure

OP Technique	**Chest wall closure**	**Paired comparison of success**
OWT-VAC n=20	12/20 (60%)	OWT-VAC vs. Mini-VAC, **p=0.034**
Mini-VAC n=8	8/8 (100%)	Mini-VAC vs. Mini-VAC-Instill, **p=0.455**
Mini-VAC-Instill n=15	14/15(87%)	Mini-VAC-Instill vs. OWT-VAC, **p=0.026**

The success rate was higher (p = 0.034, Table 12) in the minimally invasive vacuum group (8 of 8, 100%) than in the OWT-VAC group (12 of 20, 60.0%).
The success rate was also higher (p = 0.026) in the minimally invasive vacuum group with instillation (14 of 15, 93.3%) than in the OWT-VAC group (12 of 20, 60.0%). The success rates in the two minimally invasive groups were similar (p = 0.455).
The mean postoperative length of stay (LOS) in hospital of all patients was 21 days (median 18, range 6 to 51 days, Table 10). LOS was significantly shorter (p = 0.027) in the Mini-VAC-Instill group (15.1±4.8) than in the other two groups (23.8±12.3, 22.7±1.5).
The mean LOS did not differ between the primary empyema group and the postoperative empyema group (21.8 days vs. 20.6 days; p = 0.744).
Overall, the 30-day and 60-day mortality rates were 4.6% (2 of 43) and 9.3% (4 of 43), and none of the deaths was related to infection.

6.3.2. Long-term outcomes

In 9 patients, fenestrations were left open; 2 patients died before closure, 3 rejected reoperation, 4 had permanent bacterial colonization of the window, and 1 was treated with definitive OWT because of acute recurrence after primary closure.
The rest of our patients reported a very good quality of life in our outpatient interview. We performed also - regularly before and four weeks after discharge - a x-ray examination in our outpatient (Figure 14).
Finally, to obtain a written objective report about the health status of our patients we contacted the family doctor of our patients.

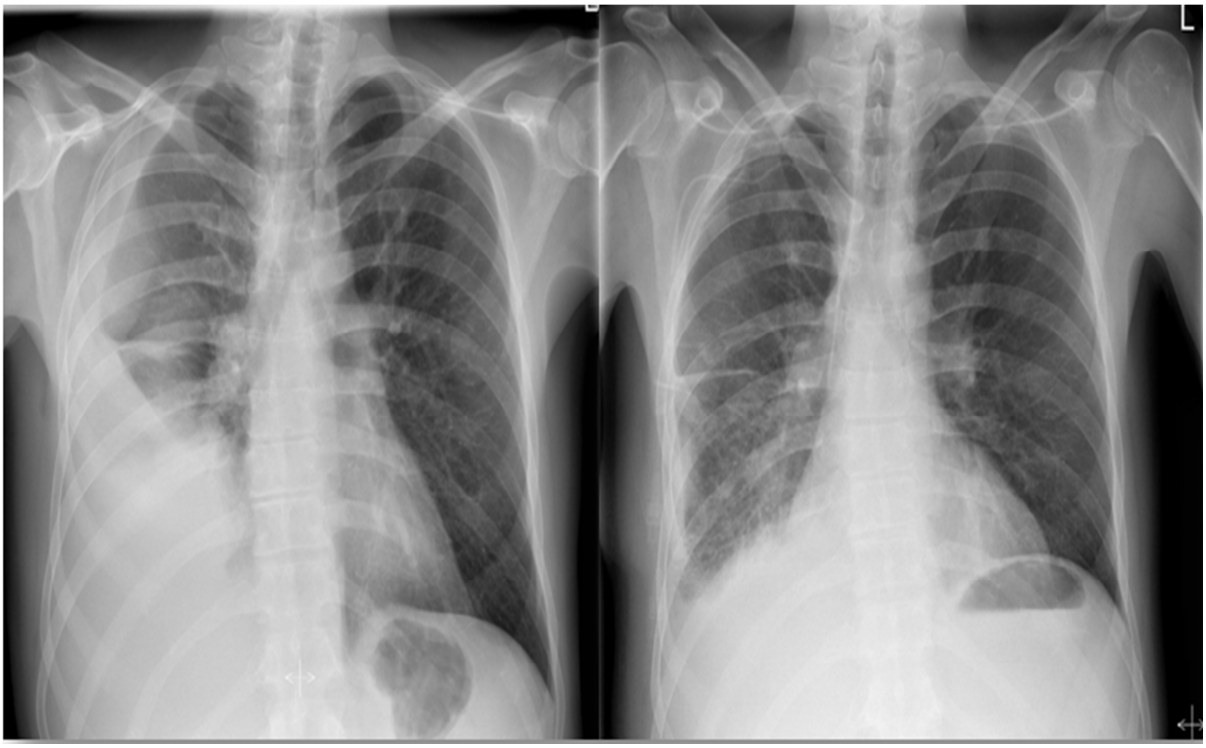

Figure 14: Praeoperative and postvacuum radiologic imaging of empyema thoracis with “restitution ad integrum”.

Overall success rate for the final closure of the chest wall without empyema recurrence was 76.7% (33 of 43).

The 1-year, 2-year, 3-year, and 4-year survival rates were 74.6%, 60%, 56%, and 50% respectively (Figure 11).

There were no significant differences in the 4-year survival rates of the three subgroups (40% in the OWT-VAC, 62.5% in the Mini-VAC, and 60% in the Mini-VAC-Instill group).

No case of death was related to intrapleural vacuum therapy. The Cox regression analysis of overall survival showed no prognostic factors (Table 13).

Only malignancy showed a slight tendency (HR = 2.37 (0.87-6.41), p = 0.091).

Table 13: Relationship between investigated factors and survival

Factors	**Survival**	
	HR (95%-CI)	**p-value**
Age	1.03 (0.99-1.08)	0.152
Malignancy (yes/no)	2.37 (0.87-6.41)	0.091
Surgery indication:		
primary empyema	reference	-
postoperative empyema	0.60 (0.22-1.61)	0.306
Empyema treatment:		
OWT-VAC	reference	-
Mini-VAC	0.66 (0.18-2.35)	0.518
Mini-VAC-Instill	0.61 (0.16-2.29)	0.460
Successful final chest wall closure (yes/no)	0.81 (0.29-2.31)	0.695

6.4. Comment

Treatment of high risk patients and near-septic or septic patients with pleural empyema is still a challenge.

Even in the case of successful empyema management, patients with multimorbidity, malignancy, and/or immunosuppression have a poorer short-term prognosis (mortality up to 15%, Table 14) and long-term prognosis with a median survival of 22.8 to 67 months [74-79] than patients without such additional complications.

Table 14: Overview; outcomes of OWT therapy in debilitated patients

Author/Year	Number of patients	Empyema cause	30-day mortality	Closure of OWT	Recurrence	OWT duration
Maruyama et al. 2001	53	primary and secondary	15% (8/53)	83% (44/53)	11% (5/44)	Mean 128.0+/- 32.1 days
Thourani et al. 2003	78	primary and secondary	5% (4/78)	definitive OWT	definitive OWT	definitive OWT
Massera et al 2009	19	primary and secondary	6% (1/17)	59% (10/17)	10% (1/10)	Median 5 (3-9 months)
Reyes et al. 2010	78	primary and secondary	6% (5/78)	22% (17/78)	6% (1/17)	Median 454 (90–1068 days)

6.4.1. Comment to short-term outcome

Minimally invasive treatment with Mini-VAC and Mini-VAC-Instill significantly reduces the treatment duration in comparison to OWT-VAC. The length of stay in hospital could also be reduced by the Mini-VAC(-Instill) procedure, although − in almost all minimally invasive treated patients (22/23) − final chest wall closure was conducted during the same hospital stay, which additionally extended LOS.

Both treatment duration and LOS were significantly reduced by Mini-VAC-Instill therapy in comparison to the OWT-VAC and Mini-VAC techniques.

Hospital stay is a complex socioeconomical and cultural issue. However, to date, only few authors have achieved similar LOS for thoracic empyema [25, 77]. Schneiter at al. reported a mean hospitalization of 18 days for early and late postpneumectomy empyema with repeated open surgical debridements and antimicrobial therapy [25]. The thorax was definitively closed in 71 of 75 (94.6%) patients. Thourani et al. treated 78 empyema patients with definitive OWT (modified Eloesser flap) and reported a mean LOS of 16 days [77]. The modified Eloesser flap procedure was intended as a permanent one-stage procedure, therefore in the study by Thourani et al., treatment duration was equivalent to LOS.

The largest literature series of OWT patients with heterogeneous but limited causes of empyema (excluding the deadliest, the postpneumectomy empyema) showed 30-day mortality rates between 5% and 15% (Table 13). The OWT procedure may result in a good prognosis in medical unstable and debilitated patients. The most common causes of death after OWT are sepsis and multiorgan failure [74-79]. In our study, we lost 2 patients due to cardiac and multiorgan failure, which resulted in a 30-day mortality rate of 4.6% (2 of 43). Therefore, VAC treatment, particularly of the minimally invasive type, offers the same survival prognosis than classical OWT treatment but a higher rate of chest wall closures.

The most important advantage of Mini-VAC and Mini-VAC-Instill therapy is probably the potential of undelayed (ie. same stay) chest wall closure after VAC treatment. In the Mini-VAC group, all thoracic windows were closed, and only one definitive fenestration was left in the Mini-VAC-Instill group. Indispensable requirements for chest wall closure were good macroscopic aspects and negative microbiological cultures. In the study by Palmen et al. [9], 50% of patients died of OWT-related complications (bleeding and recurrent infections) during follow-up (the average duration of follow-up was 46 ± 19 months)

A recent Cox proportional hazard model showed a significant association of the closure of OWTs (HR 0.31, 95 % CI 0.10–0.88; p = 0.03) with overall survival [74]. In our study, successful chest wall closure was not significantly associated with survival (HR 0.81, 95% CI 0.29–2.31; p = 0.695).

6.4.2. Comment to long-term outcome

The 4-year survival rate of all patients was 50%, and no case was related to intrapleural vacuum therapy. We found no independent prognostic factor for death or survival, and even malignancy had a p-value of 0.091 (Figure 15. Table 13).

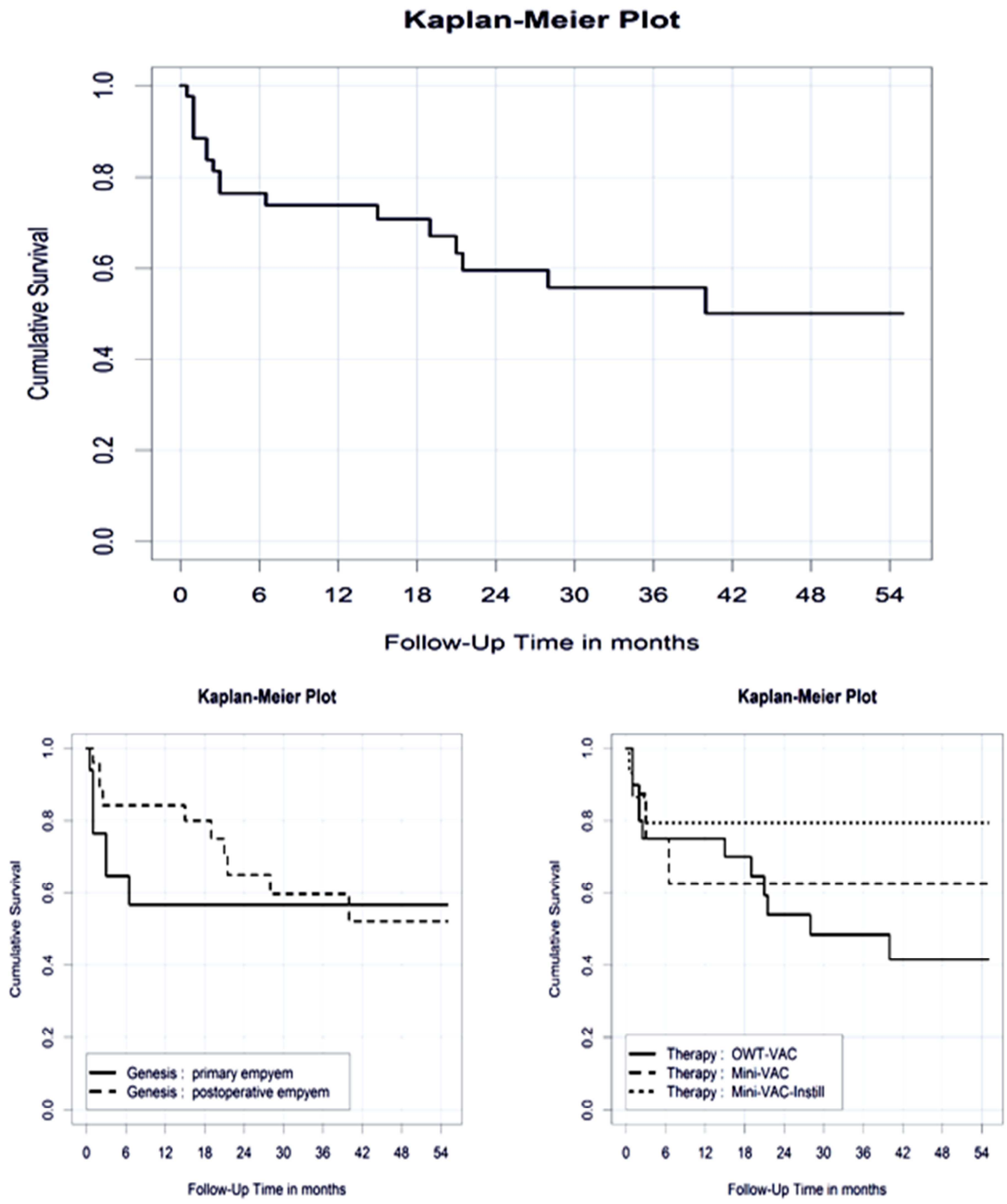

Figure 15: Cumulative and detailed survival of patients with intrathoracic VAC.

Reyes et al. achieved survival rates of 74% and 60% at 12 months and 60 months, respectively [79], when treating 78 debilitated patients with empyema with OWT. In the study by Hato et al., the 60-month survival rate of OWT patients was 34.7% (12 of 35), whereas the median survival period was 22.8 months. According to the univariate analyses, variables significantly associated with increased overall survival

included closure of the OWT (p = 0.03) and absence of diabetes mellitus (p = 0.04) [74].

The long-term survival of this vulnerable patient population is mainly determined by secondary diseases rather than by the type of treatment. Taking this fact into consideration, the primary goal should be prompt empyema therapy to enable treatment of the underlying disease.

Study limitation

The main limitations of our study are its design as a retrospective single-center study and the limited number of patients included.

6.5. Conclusions

Minimally invasive VAC treatment (Mini-VAC and Mini-VAC-Instill) fulfills the aim of a safe and fast therapy in debilitated and near-septic or septic patients with empyema thoracis.

The main advantage of minimally invasive VAC treatment is the high rate of chest wall closure within the same hospital stay.

This offers better quality of life for the patients, a very low reinfection rate, and fast treatment of secondary diseases (e.g. anti-cancer therapy).

Additional instillation therapy is particularly beneficial for septic patients with highly infected or bacterially colonized pleural empyema.

7. Pros and Cons of VAC therapy

Studies on intrathoracic vacuum therapy [58, 65] show a low adverse events rate (≤5%). In the series presented, the intrathoracic VAC and VAC-Instill treatment were well tolerated by the patients without exception.

7.1. Malignancy and VAC therapy

The U.S. Food and Drug Administration do not recommend generally to use VAC therapy in malignant wounds because it may stimulate proliferation of malignant cells [80]. Seeding of tumour in the wound (pleural carcinosis in 4 of our patients) and simultaneous intrathoracic vacuum therapy did not accelerate tumour growth in the series of 5 years presented. The stable, non expanding state was confirmed by regular chest computer tomography.

7.2. Lung fistulas and VAC therapy

The previously existing protocols contraindicating VAC in presence of bronchopleural fistulas or residual lung tissue was overwritten by the results presented. A more aggressive policy in these environments is justified. Lung fistulas and simultaneously VAC therapy was feasible due to high-tech continuous suction level of - 125 mm Hg. Fistulas closed spontaneously within 72 hours from initiation of VAC therapy. Intraoperative water-tests approved our clinical observations. To avoid direct contact of the VAC device with the mediastinum after lobectomy and pneumectomy, the area was covered with Mepitel (Mölnlycke Health Care, Erkrath-Unterfeldhaus, Germany) during the first session. No patient had vacuum therapy related complication.

7.3. VAC therapy in the resence of BPF

The presence of a smaller bronchial stump fistula (< 1 cm) was not a contraindication for vacuum-assisted closure. Larger than 1 cm BPF was resistant to VAC therapy. Further investigations have to discuss whether VAC-Instill is applicable in patients

with bronchopleural fistula, and whether simultaneous antibiotic/antiseptic flushing during VAC therapy is possible. Our recent experience with VAC and OWT support the implementation of this technique in patients with bronchopleural fistula, the role of VAC Instill has not yet been investigated. A feasibility study of ours of Mini-VAC-Instill [63] showed promising results so we extended this concept in daily clinical routine.

7.4. Empyema cavity volume and VAC therapy

No pre-existing volume of the cavity is a clear indication/contraindication of intrathoracic VAC therapy. Following effective Mini-VAC-Instill therapy, the remaining pleural space have diminishedl in all but one case (mean volume ≤303 ml). Six patients were presented with postpneumonectomy empyema and in all cases the VAC therapy was successful.

7.5. VAC therapy in the management off anaerob-infections

Previous studies defined the anaerob infection as a relative contraindication to VAC therapy [81, 28].

Mouës et al. investigated whether the positive effect on wound healing found in VAC treated wounds could be explained by an effect on the bacterial load. In conclusion, this study showed a positive effect of VAC therapy on wound healing, expressed as a significant reduction of wound surface area. However, this could not to be explained by a significant quantitative reduction of the bacterial load, whereas Staphylococcus aureus shoed a significant increase in VAC treated wounds ($p < 0.05$). On the other Hand Morykwas and Argenta showed, that the VAC therapy also leads to reduced bacterial colonisation by anaerobic organisms through increasing tissue oxygen concentrations. Neutrophils use the increased oxygen to kill bacteria. Bacterial colonisation was decreased by 1000-fold compared with non-negative pressure exposed wounds after four days of treatment [83]. My clinical findings suggest that an anaerob infection is not a contraindication for intrathoracic VAC application.

8. Vacuum-assisted closure therapy in the management of lung abscess

Having obtained positive experience in the pleural space with VAC, more complex situations were managed with VAC. Despite significant advances in the treatment of thoracic infections, complex lung abscess remains a problem in modern thoracic surgery. Large lung abscesses and anaerobic bacteria are associated with poor outcome [84]. The prognosis is poor in elderly, debilitated, malnourished, and immunocompromised patients. Abscess of the lung is characterized by a pseudomembrane, with poorly defined borders and it will be covered by granulation tissue during the healing of the surrounding parenchyma. Therefore, VAC therapy seemed to be contraindication here.

8.1. Case report

This case-management [85] was approved by the local ethics committee of the Hospital Barmherzige Brüder (Ethikkomitee am Krankenhaus Barmherzige Brüder Regensburg). A 43-year old man was diagnosed with an acute lung abscess in the left upper lobe. The patient abused alcohol and had a history of pneumonia with an intermittent febrile course. The production of purulent sputum became common within the last weeks/months. Microbiology of the sputum showed a mixture of Prevotella buccae and Bacteroides spp. The patient was started on intravenous piperacillin/tazobactam while awaiting sensitivity results. Fiberoptic bronchoscopy excluded significant airway obstruction and there was no draining bronchus of the abscess. Chest computed tomography (CT) showed a 5 to 7 cm disintegrated mass with air bubbles in the anterobasal and laterobasal segments of the left lower lobe. The abscess sat quite close to the visceral pleural surface. Because the lack of the transbronchial clearance a percutaneous catheter drainage (14 French) insertion under CT control was performed (Figure 16).

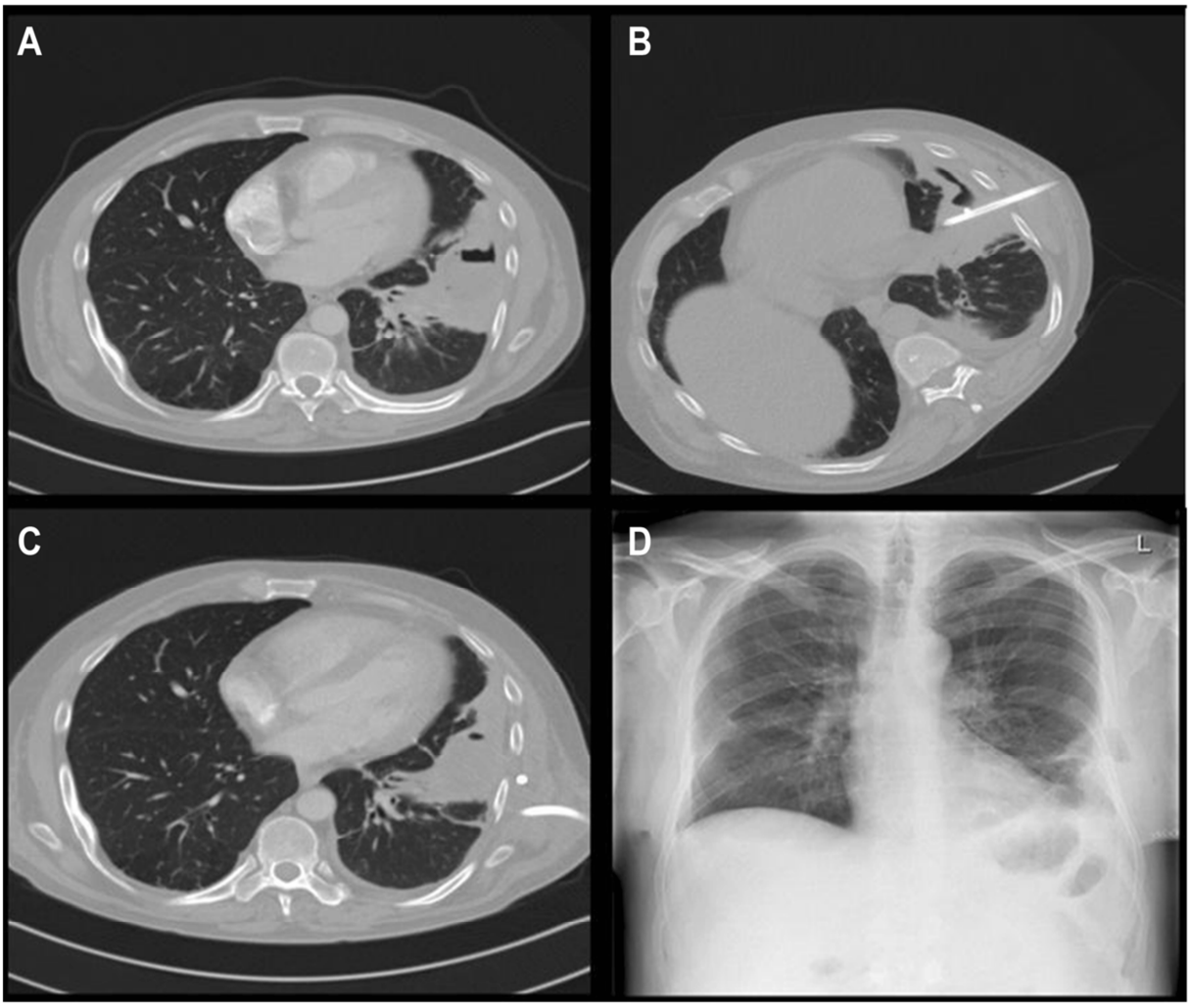

Figure 16: Morphological features of the course of conservative therapy and follow-up. (A) CT scan revealed a disintegrated mass of the left lower lobe. (B) Insertion of percutaneous catheter drainage. (C) Catheter dislocation. (D) Chest X-ray after VAC Therapy and before discharge.

A whitish-yellow substance was aspirated, and the pH of the putrid contain of abscess was acidic (pH= 6.8). Seven days after this intervention, the clinically course showed no improvement and the patient had high elevated levels of C-reactive protein. Chest CT showed catheter dislocation (Figure 16) and no reduction in abscess size.

The septic patient was planned for surgical intervention. Due to the poor general condition (Karnofsky-Index = 50%), the decision was made to proceed with Mini-VAC therapy, including an ALEXIS retractor. Under general anesthesia, a 6 cm-long incision centered under CT guidance over the area of the lung abscess was performed. The intercostal muscle was divided, and the abscess cavity was opened.

A circumscribed and open “empyema” cavity was created in terms of an abscess - pleural space - chest wall - skin communication. The surrounding lung was adherent to the parietal pleura, creating an isolation barriére.

ALEXIS retractor provided access and tissue protection.

Then, the ALEXIS retractor was positioned. After intercostal aspiration of all pus and necrotic debris, the cavity was flushed with Lavanid 0.02% (Serag-Wiessner KG, Naila, Germany). VAC sponges (GranuFoam Dressings (KCI Medical, Wiesbaden, Germany), 400 – 600 microns) were inserted in the abscess cavity through the soft tissue retractor to fill the entire intrapulmonary space. The level of suction was initially set to 100 mm Hg, with a maximum suction of 125 mm Hg. The sponge was changed once in the operating room on the 3rd postoperative day, at which point the ALEXIS retractor was changed as well. Incentive spirometry was part of therapy to facilitate remaining lung expansion. Results: After nine days of Mini-VAC treatment, the abscess healed. The remaining subcutaneous and chest wall space was filled with Genta-Coll resorb (Resorba GmbH, Nürnberg, Germany) - a hemostyptic gentamicin collagen sponge. The abscess cavity was sterile, and the mini-thoracotomy could be closed on the 10th postoperative day. The patient was discharged on the 11th postoperative day without any further complications (Figure 16.). No recurrence occurred during long-term follow-up (13 months).

8.2. Discussion

A lung abscess is a thick-walled cavity that contains purulent material and can occur at any age [86]. Approximately 90% of patients with lung abscesses can be cured by antibiotic therapy and/or guided drainage [87-88]. The roles of surgery include the prevention of sepsis and managing complications. Complicated lung abscesses are associated with high mortality rates of up to 23% [28]. Standard surgical treatment includes debridement of the abscess or even pulmonary wedge/anatomical resection and is often combined with prolonged hospitalization [28]. Here, we demonstrated the application of Mini-VAC therapy in a debilitated patient with a complicated lung abscess for the first time. The application of plastic wound retractors in managing

pleural empyemas with Mini-VAC therapy is well described. The same technique can also be easily used for the treatment of lung abscesses. An important advantage of plastic wound retractors use is that they act also as a barrier that protects the soft tissue and wound from bacterial translocation. The first installation, and perhaps the first change of the VAC system, could be performed under general anesthesia. Further changes may be performed bedside. Because a lung abscess is covered by granulation tissue during the healing of the surrounding parenchyma, no fistula in the lung parenchyma was detected, and the level of suction was steady. Secretions were collected in the VAC device. The continuous removal of potentially infectious secretions from the wound supported rapid healing of the initially septic condition. Daily cleaning or dressing was not necessary, and we changed the VAC sponge only once over the course of 7 days. This procedure was convenient for both the patient and the doctors. Outpatient service with initial daily wound care performed by specialized nurse technicians would be advised. The abscess cavity was rapidly cleaned and decreased in size. Closure of the chest was easy, without any short or long-term treatment failure.

The use of the Alexis retractor and Mini-VAC therapy for a septic patient with lung abscess is therefore a novel extension of use of negative pressure wound therapy in thoracic surgery. VAC systems should be considered for widespread use as an alternative option for the treatment of complicated pulmonary abscesses in elderly, debilitated, and immunocompromised patients after failed conservative treatment.

The abscess should be located in the relative proximity to the visceral pleural surface. It is difficult to achieve lung abscesses localized paravertebral, paramediastinal or apical positions.

Nevertheless, the intrathoracic use of VAC therapy can trigger clinically significant complications [85] and there are also some contraindications, for example: disorders of blood coagulation, ongoing pain and allergic reaction to the VAC sponge or the Instill liquids.

9. Indication for intrathoracic VAC therapy

The existing internationally accepted flow-chart (Figure 1) was revised incorporating all the present modalities in thoracic empyema treatment incl. VAC therapy (Figure 17).

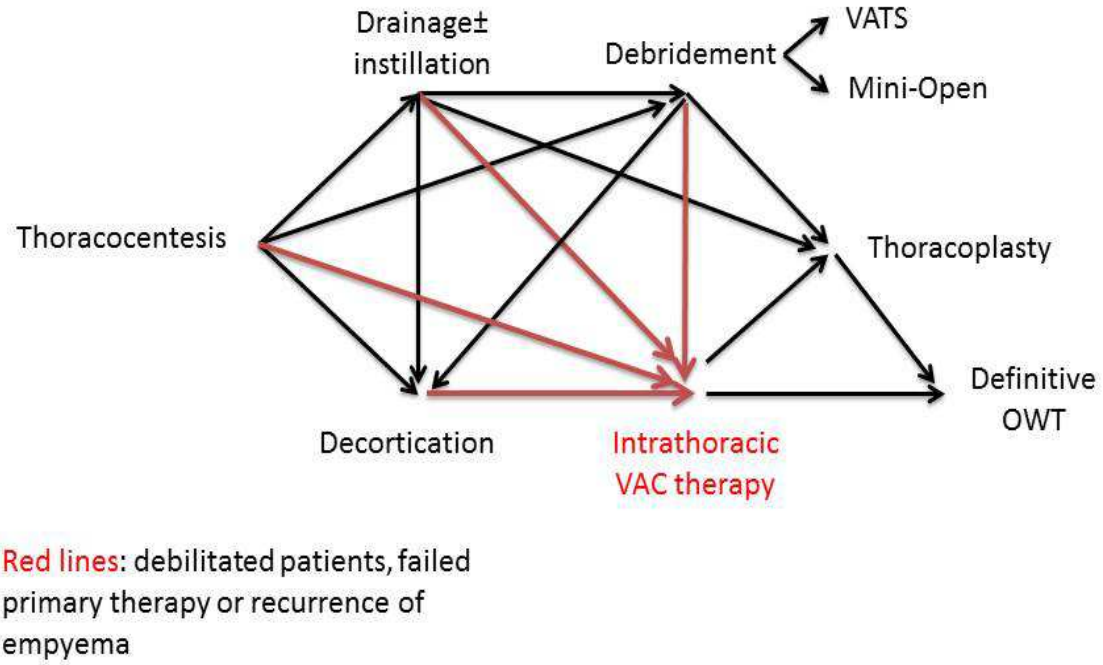

Figure 17. Treatment modalities according to the therapeutic pathways: the modified empyema diamond

For high-risk patients, (pre)septic patients with poor general condition (Karnofsky index ≤50%) and multimorbidity (≥3 organ diseases) or immunosuppression, and for patiens with postoperative, or recurrent pleural empyema intrathoracic VAC therapy is a promising option.

I recommend generally the use of Mini-VAC-Instill in the abscence of BPF.

Mini-VAC is also one of the choices if there is a permanent supply of causative organisms due to a smaller than 1 cm bronchopleural fistula.

It can be applied either as a definite treatment with intent to cure, a preliminary procedure prior to definite treatment or as a last resort procedure when others have failed to achieve a relatively stable disease.

OWT-VAC is helpful if a muscle transposition is proposed as the pleural space becomes sterile-cleansed. The studies presented support a non-delayed application of intrathoracic vacuum-closure therapy

10. Original Observations

Internationally pioneering observations in the topic and multi-peer reviewed results are forming the pillars of this clinically focused project. The data and their conclusions are presently transforming the state of art treatment protocols of Thoracic Empyema.

10.1. The results presented and their documented international acceptance prove, that the “a priori” intrathoracic vacuum therapy is a safe and simple alternative to OWT alone in the management of medical unstable patients with pleural empyema.
The most important advantages of the OWT with VAC were fast detoxication of sepsis and local control of the pleural cavity. Furthermore, the length of hospitalization was shorter in patients with immediate OWT and VAC-therapy installation.

10.2. OWT-VAC therapy on thoracic empyema was proven as a safe and efficient method as outpatient treatment, reducing costs and hospital load alike. Nevertheless, the Mini-VAC-(Instill) dressings should be routinely changed every 3–4 days, in the OT, to allow precise and continued monitoring of infection and to keep the wound for rapid secondary closure.

10.3. Intrapleural VAC therapy was proven to have a beneficial effect on the re-expansion of the remaining lung tissue following previous resection. No patient had a local complication due to local suction.

10.4. Initiation of a priori intrathoracic VAC therapy of the empyema without classical OWT was introduced and further developed by Mini-VAC-Instill technique. Using this method OWT was omitted, enabling a safe and short treatment with subsequent early chest wall closure.

10.5. An upgrade of Mini-VAC was developed with added instillation of antiseptics in invasive aggressive empyema thoracis – i.e. high agressivity bacteria and/or reduced

immunity patients. This technique is safe and highly compatible with high-risk patients.

10.6. Comparing the methods applied and analysed, OWT-VAC has equivalent efficacy to Mini-VAC-(Instill) at managing both primary and secondary (postoperative) thoracic empyema. Mini-VAC-Instill vs. OWT-VAC/Mini-VAC provide the fastest empyema clearance and healing.

10.7. It was proven by clinical series and by a clinical case report, that against the received wisdom, presence of lung tissue, bronchopleural fistula, smaller bronchial stump insufficiency, local malignancy and the lung abscess cum pleural empyema scenario is amenable for intrathoracic VAC application.

10.8. Standard pleural VAC therapy offers rapid treatment for pleural empyema combined with intraparenchymal abscess formation. The method is superior to the historically established Monaldi drainage and its derivates.

10.9. The existing internationally accepted flow-chart was revised incorporating all the present modalities in thoracic empyema treatment including VAC therapy.

11. List of Figures

Figure 8:
Postoperative aesthetic results of Mini-VAC.

Figure 9:
Decision making algorithm for debilitated patients with empyema thoracis.

Figure 10:
Mini-VAC-Instill: minimally invasive local decortication, vacuum foam insertion and periodic polyhexanid instillation. Good aesthetic results.

Figure 11:
(A) Empyema thoracis Stage II.
(B) Introduction of VAC-Instill sponge over Alexis retractor.
(C) Intrapleural VAC-Instill.
(D) Postvacuum thoracoscopic view.

Figure 12:
Automated topical solution delivery mode, here for example 95 ml polyhexanide instillation for 20 min every 4 h.

Figure 13:
Intrathoracic macroscopic view after VAC therapy: very good diffuse granulation.

Figure 14:
Praeoperative and postvacuum radiologic demonstration of empyema thoracis with restitution ad integrum.

Figure 15:
Cumulative and detailed survival of patients with intrathoracic VAC.

Figure 16:
Morphological features of the course of conservative therapy and follow-up.
(A) CT scan revealed a disintegrated mass of the left lower lobe.
(B) Insertion of percutaneous catheter drainage.

(C) Catheter dislocation.
(D) Chest X-ray after VAC Therapy and before discharge.

Figure 17:
Treatment modalities according to the therapeutic pathways: the modified empyema diamond.

12. List of Tables

13. References

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- Short-term and long-term outcomes of intrathoracic vacuum therapy of empyema in debilitated patients. Z. Sziklavari. 5. VERAFLO™ Symposium in Halle (Saale), 17.06.2016.

Köszönetnyilvánítás

A köszönetnyilvánítást érzelmi okokból magyar nyelven teszem.

Jelen disszertáció elkészültét két mesterem tette lehetővé, ezért nekik hálával tartozom.

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Szintén köszönetet mondok a Klinik für Thoraxchirurgie Krankenhaus Barmherzige Brüder minden munkatársának az értékes hozzájárulásukért.

Köszönöm előbírálóimnak a nehéz és értékes hozzájárulásukat.

Publikációimat, utazásaimat Krankenhaus Barmherzige Brüder mindig támogatta.

Külön köszönöm feleségemnek és gyermeikeimnek az éveken át tartó türelmet, a gyakori nélkülözést és a folyamatos bíztatást.